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should study compaction:
Part 1 - Introduction**

**Joint Supply Chain Actors
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Cover photo: Tablet compression machine (see Why pharmacists should study compaction: Part 1 - Introduction on page 4)



To speed or two speed: is that the question?

It is that time of the year when EIPG is busy preparing for its General Assembly – an eagerly awaited annual event that brings together our delegates from member organisations all over Europe. Last year, the Assembly in Paris was a significant one for us, as we celebrated the 50th anniversary of EIPG. We looked back on the notable changes that have taken place in the history of medicines and medicines regulation in Europe in that time span. However, the time for reminiscing is over, and, notwithstanding fond memories, it is to the future that we must now cast our attention.

This passing year has seen another significant European event – that of the 60th anniversary of the Treaty of Rome. It is, however, concerning that the anniversary of the birth of the Community comes at a time when the very ideal that engendered this reality is constantly being questioned. From the revival of the notion of a two-speed Europe to, more worryingly, the oft-repeated claim that healthcare, particularly where the accessibility to medicines is concerned, is not uniformly available to all European citizens. Yes, size matters. It matters in terms of market size and economies of scale, and it matters in terms of the resources that different countries – indeed sometimes different regions within the same country – possess in order to bring the latest life-saving medicines to patients in a timely manner at an affordable cost, be it directly to a single patient or to society in general when called upon to finance these costs to some greater or lesser extent through fiscal measures.

It is this very concern that has prompted, on either side of the Atlantic, measures, or at least the thought of them, that can achieve the objective of speeding not only the drug discovery, but also the regulatory process through which the risk-benefit



balance of medicines are evaluated before becoming available to patients. The concept of speeding the process, however, has drawn divided opinions on the subject, and whilst the idea, in general, is one worthy of consideration, concerns have also been expressed by both the pharmaceutical industry and some regulatory authorities at the potential ramifications of unduly accelerated pathways. Quality, cost and speed – the saying goes that you can have any two, but not all three, and, therefore, we should be careful of policies that advocate rushing into a path where angels would fear to tread.

Yet, not to try is not an option either. We are on the edge of exciting discoveries in medicine that are set to become a reality in healthcare even in our lifetimes. Technology is, however, potentially getting ahead of our ability to surmount challenging social hurdles, and achievements in medicine risk finding us ill-prepared. We still grapple with the problem of finding solutions to differences in accessibility to cures, when such cures are, for the larger part, aimed at curing the individual, and have yet to face the reality when the provision of a cure means that not only the individual, but also his or her progeny, will consequently have been given access to a state of health free of an illness.

Therefore, *festina lente* – make haste slowly. I look forward to meeting our member associations and guest organisations soon in Malta, so that together we can face these challenges and move forwards together, without having to accept that to speed, or two speed, are the only options available to the pharmaceutical world.

A handwritten signature in black ink, appearing to read 'Claude Farrugia', with a horizontal line underneath.

Professor Claude Farrugia
President, EIPG

WHY PHARMACISTS SHOULD STUDY COMPACTION: PART 1 - INTRODUCTION

by Michael Gamlen

Tablets remain the most used pharmaceutical dosage form by both number and volume. This is the case for a variety of reasons. The per-unit manufacturing cost of tablets is lower than any other widely available dosage form, and what human activity is not driven by cost these days? As important, they are an extremely flexible dosage which can be developed with a very wide range of final properties.

Michael Gamlen studied for a PhD with Professor JM Newton at Nottingham University and was Head of Solid Dosage Form Development at the Wellcome Foundation Ltd for 15 years. He is the inventor of the Gamlen Powder Compaction Analysis System, and works as a consultant and trainer. He is a regular contributor of articles on tableting and powder compaction.

In its current form, the tablet originates from the late 19th century when single punch tablet presses and early rotary presses became widely available. The first book on tableting I have been able to identify was written by Joseph Wood, published in 1904¹. In his introduction (p.9) he states, "The present era of compressed tablet making dates back but a few years, and during this period the quality of the tablets, as made by the highest exponents of the art, has gradually improved until it has reached a high standard." He continues (p.10) "The early tablets...were compressed hard, and made without reference to their solubility or their power to disintegrate, and little skill was required in their preparation. On the other hand, the proper manipulation of the medicinal ingredients, and the choice, proportioning and manipulation of excipients best suited to use with the different formulas, require considerable skill, as well as the intimate knowledge of the physical and chemical properties of the ingredients". It seems shocking that, despite over 100 years of research and thousands of completed PhDs, our knowledge of

the fundamentals of formulation and compaction is still, at best, limited.

As in Wood's days, the tablet is a complex drug delivery system in which the drug substance is combined with a number of excipients to aid formulation of the desired product. These include bulking agents, binders, disintegrants and coatings all of which have some function to aid the processing of the drug substance into the end-product form. The excipients and drug substance are processed through a number of unit operations, such as mixing, blending, granulation, tableting and often coating to form the final product (Figure 1).

The final tablet has to fulfil a number of characteristics, including the ability to deliver the correct amount of drug substance into the patient's system at the required rate, as well as possess physicochemical

Tablet Critical Quality Attributes
Potency/assay
Taste/chewability
Bioavailability/disintegration/dissolution/release profile
Absorption
Stability – physical, chemical
Moisture
Friability/hardness
Dispersion
Effervescence
Weight/content uniformity/mass
Related substances
Microbial

Table 1. Tablet critical quality attributes.

characteristics that make it easy to handle, administer and store. In addition, it has to meet the particular requirements of a particular type. For example, dispersible products must be of a suitable size, hardness, texture and stability, as well as taste and smell (see Table 1).

Process and formulation development of the desired tablet form is time consuming and complex because knowledge of excipient/drug substance material properties, and their relationship to the processing parameters by which the final product is made is limited, preventing *a priori* prediction of quality.

How do we know whether we will make a good tablet?

Control of tablet properties requires a powder for compaction with the requisite attributes. To take a phrase from the world of computing, "Garbage in – Garbage out!!!". An unsuitable formulation or process will result in a tablet which will cause problems in production and may not meet the required standards. The powder properties with most impact on compaction are those relating to



Figure 1. The tablet manufacturing process.



compaction or compressibility, and to lubrication. Of course, uniformity of drug distribution within the powder is also a prerequisite, and adequate flow is also required; this is generally easier to achieve.

In my view the major problem in understanding compaction and tableting has been the difficulty of studying compaction and lubrication behaviour on a laboratory scale and under controlled conditions. The key requirement here is for what I regularly refer to as a “fair test” on which to assess powder properties. Understanding of compaction has been improved by the identification of the “Compaction Triangle” by Tye *et al.*² (see **Figure 2**). As the compaction pressure used to make the tablet changes, so does the solid fraction or porosity. In addition, the tensile fracture stress (TFS) also changes. TFS, at first, seems a strange measure to include at this point. However, measurement of the TFS of a tablet (first proposed by

Fell and Newton in 1968³) has proved to be the most discriminating measure of the physical property of a tablet. For example, in their subsequent paper of 1970⁴, Fell and Newton were able to differentiate between two size fractions of the same material using TFS measurements – something which no other technique (except direct measurement) is able to do.

To understand the compaction properties of a material, three key relationships have been identified. These are compressibility, compactibility, and tableability⁵. It should be noted that compressibility and compactibility have been previously defined in other compaction contexts (such as powder metallurgy). Compressibility (solid fraction versus compaction pressure), compactibility (solid fraction versus tensile strength) and tableability (compaction pressure versus tensile strength), taken together, give a very complete

picture of the compaction properties of materials.

Making compaction measurements

The key to assessing powder compressibility is, therefore, to be able to make tablets under conditions of controlled compaction pressure (which requires compaction force measurement) or controlled solid fraction (which requires real-time tablet thickness measurement) – in other words, instrumentation of the compaction system. The lack of readily available, easy-to-use compaction instrumentation is the heart of the problem of understanding compaction.

The first instrumented tablet presses were developed by Brake (1950)⁶, a Masters student of Engineering at Purdue University. His work identified many of the key relationships we still currently measure. Shortly afterwards, Higuchi and a series of collaborators during

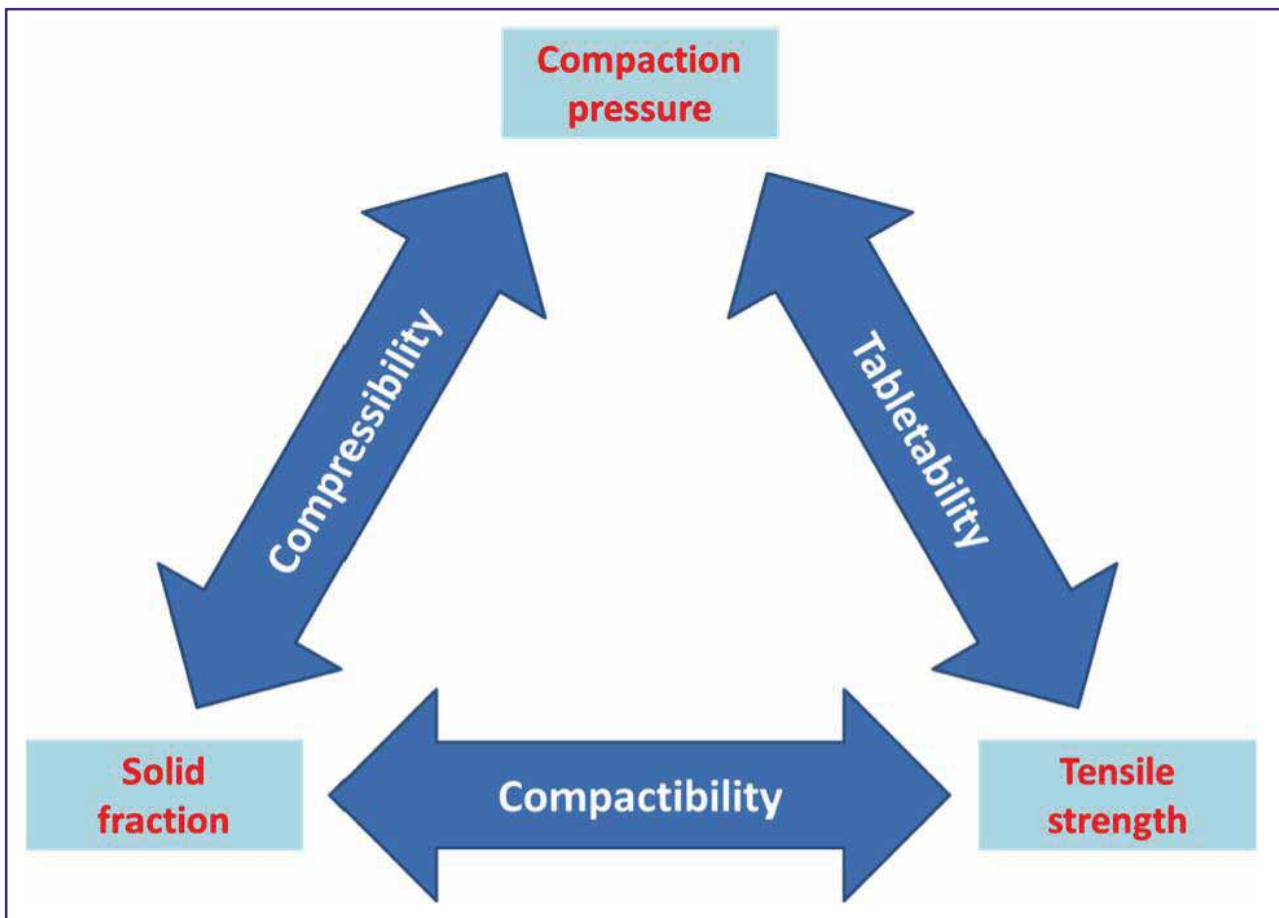


Figure 2. Compaction triangle.



the 1950s and 1960s began a seminal series of papers⁷ (16 in all!) on the physics of tablet compression. These set out the fundamental understanding of tableting behaviour and include the principles of many of the systems of evaluation still in use today.

Work in the USA and Europe in the early 1960s resulted in instrumentation of rotary tablet presses using a variety of approaches. The design of a rotary tablet press makes the direct measurement of compaction force and punch position rather problematic as you cannot easily make a direct electrical connection between the moving punch and a static instrumentation system. The approaches taken can be split into those which used measurements at a static location that were believed to give a measure of punch force, and those which used a telemetry system to broadcast electrical signals of punch force and position.

Both approaches have severe limitations. The measurement locations available for static measurement of punch force are not particularly close to the punch and are subject to considerable distortion, and cannot be validated accurately. Punch position cannot be detected at all using the static measurement approach. Although radio telemetry systems achieved a certain amount of commercial uptake, this was not sufficient to achieve widespread adoption.

The one approach which addressed both of these issues was the instrumentation of the Betapress by Ridgway Watt, Seager and Rue at Beechams Pharmaceuticals (a system to which I also contributed), which used instrumentation grade slip rings to take electrical signals off the turret of the press. These were used to measure upper and lower punch force and displacement, and were used to calibrate static load cells for the measurement of precompression and main compression force. Unfortunately, only peripheral references to the

system were published, with no detailed data. However, I can say that the system worked extremely well.

The next instrumentation system to consider is the compaction simulator. As rotary presses consume large amounts of material, many major pharmaceutical companies in the 1970s began to develop machines to try to simulate the movement of the punches of a rotary tablet press but on a single punch system. The first of these was published by Rees *et al.* using an Instron testing machine⁸. This was followed by publications on the ICI Pharmaceuticals system. A number of other companies at the time also developed systems as well as some universities, including Copenhagen⁹.

The systems relied on multi-stage hydraulic presses (two or three depending on the supplier) which were programmed to follow a signal which supposedly represented the movement of the punch on a rotary press, including the precompression, compression and ejection phases. Unfortunately, when subject to rigorous analysis, it was found that (a) it is not possible to accurately measure the position of the punches on a rotary press operating under load, and (b) the machines could not accurately reproduce the movements of the punches anyway.

Working on the compaction simulator at the Wellcome Foundation Ltd in Dartford, with Professor T M Jones, Dr A Ho and Mr A Milham, we developed a different way to work. The objective of testing powders is to discriminate between good and bad products. These might originate in a number of different ways – different batches of drug substance, different excipient grades, different moisture contents, different manufacturing processes... All need to be assessed as good or bad. We found that, by using a simple linear test profile that the simulator could accurately follow, we could see the small differences in compression

properties that were needed to assess powder compaction.

The use of compaction simulators continues to this day; successors of the two original (UK based) manufacturers remain in business and an additional group based in France also offer a servo-mechanical based system. However, the cost of purchase and the operational requirements mean that compaction simulators cannot be regarded as routine laboratory purchases.

In future articles in the series, I will be discussing how instrumented powder compaction systems can be used to optimise research and development decisions in salt selection and early formulation selection; improve the formulation process; assist with technology transfer; and improve compliance with the Food and Drug Administration Process Validation requirements.

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JOINT SUPPLY CHAIN ACTORS STATEMENT ON INFORMATION AND MEDICINAL PRODUCTS SHORTAGES

by AESGP, EAEPC, EAHP, EFPIA, EIPG, GIRP, Medicines for Europe, PGEU

Shortages of medicinal products are a growing issue of concern across the European Union (EU)¹⁻³ and indeed globally (2012, 2014)⁴. There is increasing evidence that shortages occur across the EU and that a wide range of medicines are affected⁵⁻¹⁰. Several factors can give rise to the cause of medicines shortages⁸⁻¹¹. The causes of shortages are understood to be multifactorial, including problems in production, global consolidation of manufacturing, unintended impacts of pricing and tendering policies, as well as problems within the supply chain. This paper does not expand further on issues of causation and, by extension, solution. Rather, it addresses the need for better information collection, communication and transparency in order to: ameliorate patient care impacts via improved management of shortages; and, to enhance understanding of the extent and nature of medicines shortages.

Despite steps already taken to address some of the causes of medicine shortages, the problem persists. It is clear that without reliable information, regulators, industry, parallel distributors, pharmaceutical wholesalers, health professionals and, of course, patients cannot take steps to limit the negative effects that interruptions in medicines supply have upon patient care and health system performance.

European associations representing manufacturers of medicinal products, parallel distributors, pharmaceutical wholesalers and pharmacists have come together to work jointly on proposed principles for improving collection, communication and transparency of information on shortages of medicines¹². Everyone is in agreement that reliable

information systems are an essential step in communicating the problems of shortages. Whilst it is recognised that such systems need to be implemented at national level and, therefore, to be responsive to specific national concerns and regulation, a number of principles underpin efficient, effective and reliable information systems.

Our primary concern, and the main motivation for forming this joint statement, is the health and wellbeing of patients. It is our ethical and public duty as actors within the pharmaceutical supply chain (manufacturers, parallel distributors, pharmaceutical wholesalers and health professionals) to minimise the impact of shortages, where we are capable of doing so. This statement is part of this process and focuses solely on one issue of potential redress: improved information

collection and publication about shortages.

Better information about medicines shortages is required in order to:

- Put in place contingency solutions to minimise negative impacts to patient care (e.g. initiate urgent communication to prescribers/pharmacies/wholesalers and preparation of bespoke out-of-license or magisterial products)
- Enable best management and distribution of existing stocks
- Provide verified and meaningful information to patients about why a disruption, delay or change in their therapy is necessary, and when resumption of supply is anticipated
- Implement a rapid alert and solution finding process between the Supply Chain Actors in urgent cases with severe health-related implications
- Improve understanding of the nature of the problems, the balance of causes and main policy dynamics to be addressed to prevent shortages occurring in the first place
- Mitigate the impact on patients by providing clear and properly evaluated information for communication with healthcare professionals (e.g. the INN) to facilitate:
 - Generic substitution^a or, where this is not an option
 - Therapeutic alternatives^b

The purpose of this statement is to outline guiding principles about medicines shortages information and to make recommendations on the specific features of the ideal information systems. We hope that these recommendations will help to enhance systems at the national level, and potentially form the basis of future European level action. (Examples of best practice, illustrating the principles of the paper, are provided in **Annex 1**.)

^a Where permitted by national rules

^b In consultation with, or with referral to the prescriber



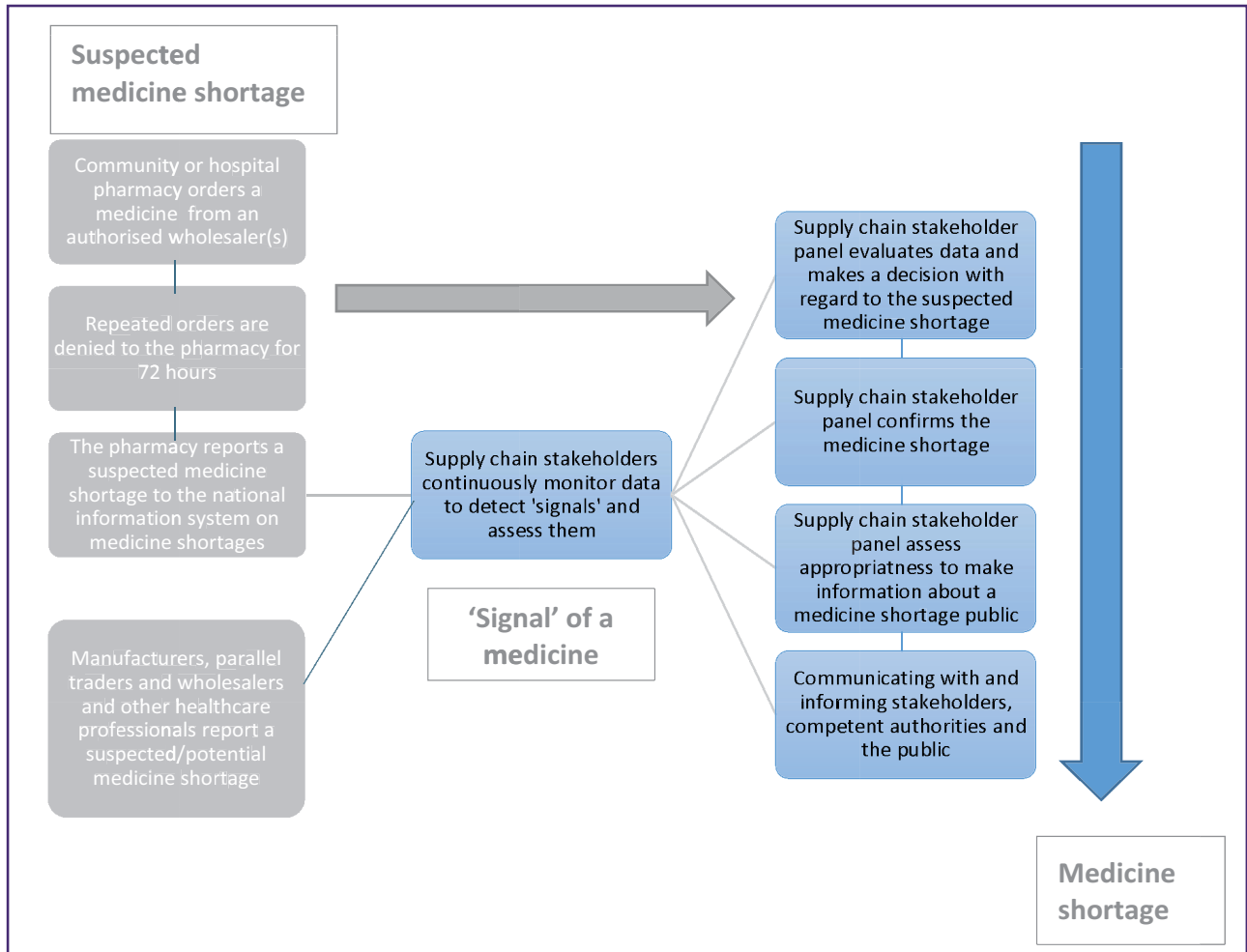


Figure 1. Potential system of detection and assessment of a medicine shortage..

Principles

Detection and assessment of a shortage^c

There is no universally accepted definition of a medicine shortage in Europe. For the purpose of setting up an effective information system of medicine shortages, we suggest a conceptual approach (see Figure 1) that would lead to early detection of shortages upon appropriate assessment of reports of suspected shortages, and ultimately will help to understand and prevent medicine shortages related problems.

For this kind of system to work, it

is important to define a ‘suspected medicine shortage’ and establish a simple mechanism to assess a ‘signal’ and decide on whether it is an actual medicine shortage. We adopt a patient-centred view in defining a ‘suspected medicine shortage’ and, as such, we define a suspected medicine shortage, for the purposes of an information and reporting system, as “the inability for a community or hospital pharmacy, as a result of factors beyond their control, to supply a medicinal product to a patient within a defined period, for example

72 hours”^d. While creating such a definition, it should be noted that it is the impact on patients arising from the unavailability of the medicine they require that is paramount. Therefore, we believe that it is important that all suspected shortages of medicines are recorded whether they are single or multi-source products.

The report of suspected medicine shortage does not necessarily mean that a medicine is in short supply. The evaluation of signal(s) of a potential shortage is required to establish whether or not there is a

^c Section 1 should not be taken in isolation. We note that the EMA is leading work at the European level to develop definition(s) for medicine shortages in collaboration with supply chain stakeholders and we strongly support this effort to ensure harmonised definitions, which, in turn, should enable comparing data within and between countries in order to understand the root causes of shortages better¹³. Under the auspices of the work led by the EMA, industry trade associations have also proposed a definition of “meaningful [supply] disruption” for European use, which refers to disruptions due to manufacturing or quality issues, which may or may not result in shortages¹⁴.

^d Agreed definition by the Supply Chain Actors Working Group on 8th July 2015, adapted definition from the French Public Health Code and later adopted in the Decree on Medicine Shortages <https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000032922434&categorieLien=id>



potential negative public health impact arising from shortage of medicine.

Another important factor to consider when assessing a suspected shortage is whether the product is multi-source or single-source. In general, if the product is of multi-source origin (and can, therefore, be substituted by another product where permitted) then this may be decided not to be recorded as an actual shortage.

Additionally, the nuances of national reimbursement and substitution rules need to be taken into consideration. Whilst respecting Member States' competencies in the domain of substitution and reimbursement, we believe that, in the case of shortages of specific reimbursable medicinal products, national reimbursement rules should not impede the provision of alternative medicines to patients.

All supply chain actors involved in supply of the concerned product should take part in the assessment of a suspected medicine shortage (a supply chain stakeholder panel) and ensure that the most up-to-date information on a medicine is made available.

In cases where a medicine shortage is confirmed, a supply chain stakeholder panel may decide to make this information public and provide further information to authorities and patients.

Sources of information

Visibility of supply information and awareness of shortages across the supply chain must be improved to allow a more responsive reaction to interruptions in supply. For example, manufacturers will be aware of a potential supply disruption of their products due to manufacturing/quality issues which are obliged to be reported to Competent Authorities following EU legislation (cf. **Annex 2**). Sometimes pharmacists experience or foresee supply difficulties before the industry or wholesalers are aware that there is, or will be, a problem.

We believe that information systems should, therefore, be open

to reports from manufacturers, wholesalers, parallel traders, pharmacists and other healthcare professionals, with reference to the origin of reports of suspected shortages. We are also aware that in an age of widespread use of social media and mobile technology, patients/the public are increasingly taking a more active role in their care. As such, it is desirable that information systems give thought to a mechanism for patient engagement where appropriate (e.g. the potential to signal a suspected shortage, as is the case for the Farmanco system in the Netherlands¹⁵).

It is important to reference the origins of reports of suspected shortages, e.g. whether they are from Supply Chain Actors, public authorities or elsewhere in order to help to evaluate the accuracy of the reports. We recognise that some reports may be inaccurate – for example, they may be out of date. Reports, therefore, should, where possible, be verified with relevant Supply Chain Actors (e.g. via a Supply Chain Stakeholder Panel). The process of verification does not grant Supply Chain Actors a veto over the suspected shortage reports. Disputes about the veracity or accuracy of a report could be settled by agreement among Supply Chain Actors in accordance with a national Supply Chain Actors' Code (see "A Supply Chain Actors Code" section).

In order to aid clear and consistent reporting of suspected shortages, a standardised reporting template is suggested and the reporting template of the Parenteral Drug Association in their Technical Report No. 68 (TR 68) Risk-Based Approach for Prevention and Management of Drug Shortages provides a good case study¹⁶.

Level of access

Patients and the public, the ultimate payers of medicine, need timely access to medicines. They also require access to information from their healthcare professional and other sources to support the use of their medicines. In the case of a

medicine shortage, patient organisations may be involved in mitigating potential risks and help to support patients with information and advice.

Principles of disclosure and transparency are being adopted in a number of areas in the pharmaceutical sector as a whole. In this spirit, we believe that access to information on confirmed shortages should be generally made available where appropriate. Information should be collated and appropriately assessed, verified, non-alarmist, non-prescriptive and made available to all who provided it.

There is a potential that wider general access to certain information may in itself lead to supply distortions, possibly exacerbating or even causing shortages¹⁷. Therefore, only verified information should be made available. The potential for such distortions needs to be addressed within an appropriate ethical context during the assessment process, and should not be considered a blanket objection to open access.

Beyond this, we believe that open access to verified information about medicines shortages should be the default position of information systems, such as that of the Food and Drug Administration (FDA), the American Society of Health-System Pharmacists (ASHP) and the European Medicines Agency (EMA) at international levels^{18,19}, with restricted access imposed only on reasonable and justifiable grounds, on an *ad hoc* basis, and in accordance with a national Supply Chain Actors Code. Assurances should be established about the information flow and where the publication of specific information should be restricted to Supply Chain Actors, as fear of inappropriate publication of certain sensitive information may act as a disincentive to its disclosure.

To avoid the potential for misattribution of blame by lay readers of the database, information about known, or indeed unknown, supply disruption causes should be

provided, e.g. “temporary disruption to manufacturing process by required upgrade”, “no disruption at manufacturing level”, “unknown supply chain problem”.

Content

We believe that information systems should be as reliable, up-to-date and as comprehensive as possible. It should allow identification of the medicinal product in short supply (in accordance with the principles above, this should be by brand where appropriate), and where possible the cause and likely duration of the shortage.

Information systems should ideally contain forms of archiving to enable an overview of trends in shortages to be provided. This can further enhance public understanding of the nature of the problem and help to better direct policy interventions. An example of this is provided by the University of Utah monitoring and analysis of drug shortages over time in the USA, providing new insights into the nature of the problem and where the best focus of long-term policy resolution may lie.

We also believe that if a medicine suspected to be in shortage has an alternative, i.e. via generic substitution^e or, in the case of a proprietary non-prescription medicine, there is an alternative with the same ingredients available, the unavailability could still be reported as a suspected shortage by healthcare professionals or wholesalers. This is because wholesalers are not allowed to substitute orders and, in some cases, pharmacists require proof of a shortage in order to enable substitution and, in the case of the over-the-counter (OTC) medication, the information held on the database (for example, the expected duration of delay) could be used to inform their patients when their preferred proprietary OTC medicine will be available again for purchase. As such, this could facilitate the work of pharmacists in finding the appropriate replacement therapy or action, and treatment of patients will not be interrupted. Pharmacists, with

their knowledge of medicines and products, may be in a position to offer training or support to other professionals on the correct selection and use of substituted products.

Alternative treatments

The effects of shortages can be mitigated if patients have access to suitable alternatives, either by way of generic substitution or the use of therapeutic alternatives as appropriate. Generic substitution, where possible, has been demonstrated to be an important solution to medicines shortages.

The Royal Dutch Pharmacists Association’s (KNMP’s) “Farmanco” system reports that 62% of shortages in the Netherlands are effectively managed through substitution with generic medicines²⁰. The multi-source nature of generic medicines means that this might entail substitution of a branded medicine for a generic, a generic for a branded medicine or one generic for another.

In order to respect:

- (i) Member State’s competencies in regulating the dispensing of medicines,
- (ii) the professional autonomy of the healthcare professionals involved, and
- (iii) the desire for patients to be involved in their own care,

we believe that information systems should not suggest specific alternative products, whether they are multi-source substitutes or therapeutic alternatives. Instead, the systems should simply indicate whether alternatives are available from one or more suppliers, allowing decisions regarding substitution and therapeutic alternatives to be made at practice (pharmacy and prescriber) level.

Governance

Supply Chain Actors are fundamental to the provision of information. As argued above, we believe Supply Chain Actors have a duty to mitigate the effects of

shortages. Where information systems are not in place at national level, we believe that Supply Chain Actors should be proactive in cooperating to develop and/or advocating for such systems.

Supply Chain Actors’ involvement in the governance of information systems – including the participation of patients – would help to ensure that systems are broadly based, responsive, efficient, user-friendly and ultimately meeting primary needs. Ideally, systems should have a level of coordination with each other in order to enable improved understanding of the international nature of medicines shortages. We recognise that national competent authorities have a role in the governance of information systems for medicines shortages (as cited in the examples below). Partnership between authorities and Supply Chain Actors may be preferred in some Member States, and is strongly welcomed by Supply Chain Actors. In order to facilitate the flow of information and reporting, we recommend that definitions are harmonised both nationally and at European level. We believe that for an effective system, there should not be any barriers to reporting of suspected shortages by healthcare professionals and wholesalers.

However, we believe that the principles laid out in this statement are essential to ensure that information systems are truly effective, and, therefore, should also be respected by national competent authorities.

Competition rules

We recognise that collaboration between Supply Chain Actors potentially gives rise to competition law issues, especially in the market-based manufacturing sector. Supply Chain Actors should be aware of their obligations in this respect, and should seek legal counsel where appropriate. It is of paramount importance that any initiatives by Supply Chain Actors are undertaken

^e Where permitted by national rules



in the public interest with the sole objective of improving the provision of information on shortages.

A Supply Chain Actors Code

Given the potential consequences for patients of an inability to access medication, shortages of medicines are both a practical and a moral problem.

Collaboration between national Supply Chain Actors to provide information systems should be underpinned by a Code of collaborative action. The Code should address, as a minimum:

- (i) the provision of information to the system;
- (ii) removal of information from the system;
- (iii) advisory timeframes;
- (iv) verification of information;
- (v) procedure of assessment of suspected shortages;
- (vi) withholding of information from the system which may have detrimental effects;
- (vii) making information on medicine shortages public;
- (viii) mutual assistance to mitigate the effect of shortages; and,
- (ix) resolution of disputes between Supply Chain Actors.

Recommendations

European associations representing manufacturers of medicinal products, parallel distributors, pharmaceutical wholesalers and pharmacists have come together and are in agreement that reliable information systems are an essential step in communicating shortages. While it is recognised that such systems need to be implemented at national level, and, therefore, to be responsive to specific national concerns and regulation, a number of principles underpin efficient, effective and reliable information systems.

1. **Transparency** in the supply chain is crucial to mitigate shortages before they arise. Supply Chain Actors on national level should, therefore, have a tool to communicate openly

and without barriers.

2. **Detection and assessment of medicine shortage:** Reporting of suspected medicine shortages is encouraged in a similar spirit to the reporting of suspected adverse drug reactions. 'Signals' of medicine shortages can then be periodically assessed by, for example, a national Supply Chain Actor stakeholder panel to establish if signals are suspected or actual shortages.
3. **Information source:** In order to aid clear and consistent reporting of suspected shortages, a standardised reporting template is suggested. Information systems should be open to reports from manufacturers, wholesalers, parallel traders, pharmacists and other healthcare professionals, with reference to the origin of reports of suspected shortages. Reports, where possible, could be verified with relevant Supply Chain Actors, but in any case, have to be confirmed prior to considering any form of publication.
4. **Level of access:** In order to aid mitigation of shortages, access to information on suspected shortages should be made available to all Supply Chain Actors. Access to information on verified shortages should be generally available to the public where appropriate and meaningful and restricted access imposed only on reasonable and justifiable grounds, on an *ad hoc* basis, and in accordance with a national Supply Chain Actors Code. Information should be collated and verified, non-alarmist, non-prescriptive, meaningful and made available to all who provided it. Patient organisations may be involved in mitigating potential risks and help to support patients with information and advice.
5. **Content of information system:** Information systems should be as reliable, up-to-date and as

comprehensive as possible.

They should allow identification of the medicinal product in short supply (by brand where appropriate), and, where possible, state the cause and likely duration of the shortage (also causes arising from outside the supply chain, such as pricing and reimbursement issues). The systems should indicate (where appropriate) whether alternatives are available from one or more suppliers, allowing decisions regarding substitution and therapeutic alternatives to be made at practice level.

6. **Governance:** Supply Chain Actors should be proactive in cooperating to develop and/or advocating for such systems at national level. Partnership between authorities and Supply Chain Actors is strongly encouraged by Supply Chain Actors. Collaboration between Supply Chain Actors to provide information systems should be underpinned by a national Code of collaborative action.
7. **Competition rules:** Supply Chain Actors should be aware of their obligations in this respect, and should seek legal counsel where appropriate.

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AESGP (The Association of the European Self-Medication Industry) is the official representation of manufacturers of non-prescription medicines, food supplements and self-care medical devices in Europe. The AESGP was founded in 1964 to contribute to the improvement of responsible self-medication at the European level and to ensure that the value of responsible self-care is recognised in pharmaceutical, food and health matters.



EAEPC (The European Association of Euro-Pharmaceutical Companies) is the representative voice of pharmaceutical parallel distribution in Europe. Through national association or individual company membership, it encompasses over 85 firms from 22 countries in the European Economic Area (EEA). The EAEPC's primary aims are to safeguard the free movement of medicines, as laid down in the EU treaty, and to counteract any attempts to restrict the freedom of choice for the consumer through trading patterns in breach of European competition law. The Association believes that free trade will lead to improvements in health standards through the provision of innovative medicines at lower cost, benefiting statutory healthcare systems, other third-party payers, and the public as both patients and taxpayers, as well as assisting the EU to achieve its objective of a single, internal market. More information is available at: www.eaepc.org



EAHP (The European Association of Hospital Pharmacists) represents c. 21,000 hospital pharmacists across 35 European

countries. More information about its activities in respect to medicines shortages is available at: <http://www.eahp.eu/practice-and-policy/medicines-shortages>



EFPIA (The European Federation of Pharmaceutical Industries and Associations) represents the pharmaceutical industry operating in Europe. The EFPIA is the voice on the EU scene of 1900 companies committed to researching, developing and bringing to patients new medicines that will improve health and the quality of life around the world.



EIPG (The European Industrial Pharmacists Group) is a European association representing the national, professional organisations of pharmacists employed in the pharmaceutical or allied industries of the Member States of the EU, the EEA, or European countries having a mutual recognition agreement with the EU on compliance control of regulated medicines.



GIRP (The European Healthcare Distribution Association) is the umbrella organisation for pharmaceutical full-line wholesalers and distributors of healthcare products and services in Europe. It represents the national associations of over 750 pharmaceutical wholesalers serving 32 European countries, as well as major international and pan-European healthcare distribution companies. GIRP members employ over 140,000 people and distribute around 15 billion packs of medicines as well as a wide range of healthcare products per year. As the vital link in healthcare, they are committed to developing and providing innovative and efficient healthcare products and services to improve health and wellbeing of patients across Europe.





Medicines for Europe (formerly The European Generic and Biosimilar Medicines Association) represents the generic, biosimilar and value-added medicines industries across Europe. Its vision is to provide sustainable access to high quality medicines, based on five important pillars: patients, quality, value, sustainability and partnership. Its members employ 160,000 people at over 350 manufacturing and research and development sites in Europe, and invest up to 17% of their turnover in medical innovation.



PGEU (The Pharmaceutical Group of the European Union) is the association representing community pharmacists in 32 European countries. In Europe, over 400,000 community pharmacists provide services through a network of more than 160,000 pharmacies, to an estimated 46 million European citizens daily. The PGEU's objective is to promote the role of pharmacists as key players in healthcare systems throughout Europe and to ensure that the views of the pharmacy profession are taken into account in the EU decision-making process.

Annex 1: Examples of best practice

Full practice examples are provided below. There are traditionally two types of information systems available, namely ones led and set up by stakeholders and government-led systems. Note: information is based on the state of affairs at the date of the publication of this joint statement.

A. Stakeholder-led system examples

Austria

There are two information systems in Austria.

System 1

1. **Detection and assessment of medicine shortage:** The system is

operated by Datacare and provides a web-based interface which facilitates communication between pharmaceutical manufacturers and wholesale distributors for making wholesale distributors aware of the likelihood of a shortage and/or reporting effective medicine shortages to pharmaceutical wholesalers.

2. **Information source:** In the event of a wholesale distributor experiencing a stock-out, the concerned wholesaler initiates a request for the manufacturer to upload information onto the database. Manufacturers can proactively upload information onto the database.

3. **Level of access:** It is accessible to wholesale distributors and pharmaceutical manufacturers. Information is passed to pharmacies in the event of a stock out at the level of the wholesale distributor.

4. **Content of information system:** The following content appears in the system – reason for delivery problem; explanation for shortage; estimated duration of supply disruption; contact person (if possible); and helpful information for healthcare professionals.

5. **Governance:** The system is operated by Datacare, a company owned by the wholesale distributor association PHAGO in conjunction with pharmaceutical manufacturers (Pharmig).

System 2:

1. **Detection and assessment of medicine shortage:** The system is based on the online publication called "index of medicines" to which a 'box' was added for the purpose of informing about shortage. The box is populated by the manufacturer – including probable length of shortages, potential replacement, cause, and contact person for additional questions.

2. **Information source:** Information is provided by pharmaceutical manufacturers.

3. **Level of access:** System is accessible to all health

professionals and supply chain operators in the case that they are customers of the publishing company of "index of medicines".

4. Content of information system:

The following content appears in the system – product name; probable duration of the shortage; potential replacement; cause of the shortage; and a contact person for questions.

5. **Governance:** The system is operated by pharmacies (hosted by Österreichischer Apothekerverlag) in conjunction with pharmaceutical industry (Pharmig).

France

1. **Legal basis:** Supply chain operators have the following obligations due to Health Law 2016-41, decree 2012-1096 and decree 2016-993.

2. • Manufacturer/marketing authorisation holder (MAH) must inform ANSM (L'Agence nationale de sécurité du médicament et des produits de santé) of any stock out or risk of stock out for medicinal products of major therapeutic interest.

• MAH informs the supply chain actors in case of stock out for medicinal products of major therapeutic interest.

• ANSM publishes the information available on its own website. The information remains visible for the duration of the shortage.

• Full-line wholesalers must inform manufacturers of any shortages not notified by the ANSM.

• MAHs have to make available a call-centre (or an equivalent organisation, e.g. 'DP-Ruptures system') in order to manage the shortages and supply medicines in case of emergency.

A shortage is defined as the impossibility for a pharmacist, after asking two wholesalers, to dispense a medicine for 3 consecutive days.

3. **Information source:** All Supply Chain Actors (manufacturers, wholesalers, community or hospital pharmacists) can notify shortages experienced at their



level, both top-down and bottom-up to the 'DP-Ruptures' system. Pharmacists are encouraged to notify shortages through an automated system.

4. **Level of access:** System allows:

- Communication with the Medicines Agency: for manufacturers; notification of a shortage or risk of shortage; dialogue with the Agency in terms of shortage management; and traceability.
- Communication with customers: top-down information dissemination in relation to anticipated shortage management; upward transmission of information allowing centralisation of notifications of observed shortages; reactive information in answer to the notification of an observed shortage.

5. **Content of information system:**

Company, product name, type of medicine ("of major therapeutic interest" or not), foreseeable date of shortage, cause of the shortage, expected date of availability, possible alternatives; in addition, in the communication with the French Medicines Agency (ANSM) only: market share, stocks available, measures included in the Shortage Management Plan (if applicable) including corrective solutions (such as generics, alternative treatments, importation, etc.).

6. **Governance:** The French regulatory body for all pharmacists (Ordre national des pharmaciens) uses and hosts an existing IT network connecting all supply chain actors (community pharmacies, hospital pharmacies, full-line wholesalers, manufacturers) and health authorities. This network, originally developed to support shared medication records, has since come to support rapid information exchange systems on batch recalls and safety alerts. The build-on system called "DP-Ruptures", was launched in February 2013 by the Ordre, followed by a pilot phase from August 2013 onwards. Since

October 2014, the service is being gradually deployed. In September 2015, around 3000 community pharmacies and hundreds of hospital pharmacists are involved in the system, as well as 55 manufacturers and health authorities (Medicines Agency, plus eight Regional Health Agencies). As the "DP-Ruptures" system is usable on a voluntary basis, the exchanges with ANSM can be made by e-mail (Rupture-stock@ansm.sante.fr) and the information with customers can be made through the call-centre. Completing the system, the agency publishes its notification on its own website.

The Netherlands

1. **Detection and assessment of medicine shortage:**

Submissions are usually made by pharmacies and each submission is checked by the respective MAH.

2. **Information source:**

The submission system is open to reports from manufacturers, wholesalers, pharmacists, other healthcare professionals and patients.

3. **Level of access:** The Dutch system allows for public access to the information.

4. **Content of information system:**

The following content is contained in the system: product name; reason for shortage; expected date of availability, and possible solution for patients (substitution, compounding, importing, and possible alternatives). The information remains visible in the system for the duration of the shortage plus one additional month.

5. **Governance:** The system operating in the Netherlands ("Farmanco") is hosted and governed by KNMP – the Royal Dutch Pharmacists Association.

Portugal

1. **Detection and assessment of medicine shortage:** The system automatically registers the information on medicines not delivered to pharmacies by

wholesalers. This automatic registry is done during the process of reception and verification of orders delivered to pharmacies. The information is used by CEFAR (Centre for Health Research and Evaluation) to produce a report every month.

2. **Information source:** Shortages notifications by pharmacies to the National Association of Pharmacies (ANF) are on a voluntary basis, although 65% of pharmacies participate in the system daily.

3. **Level of access:** ANF keeps the history of shortages from the beginning of the system. The information is sent by CEFAR to the national agency (Infarmed).

4. **Content of information system:**

The file created in the process by Sifarma (pharmacy stock management and dispensing software) is sent to ANF where the daily information is collected including name, strength, pharmaceutical form, package size and price, name of the MAH, name of the supplier (wholesaler), number of units in shortage.

5. **Governance:** System is developed and supported by ANF. The pharmacy system is hosted at the IT department of ANF.

Spain

1. **Detection and assessment of medicine shortage:**

Information Centre on Supply of Medicines (CISMED) established by the Spanish General Pharmaceutical Council manages the information sent directly by pharmacies to the regional pharmaceutical councils. The information is communicated through the application of pharmacy order management system. Information is registered in the system when order of goods has been denied by all wholesalers that pharmacy works with and pharmacy gets response message "There are no stocks".

2. **Information source:** All pharmacies are connected to the information system.

3. **Level of access:** Regional pharmaceutical councils receive



information about supply disruptions in the province and refer aggregated information to the General Council. The data is then consolidated, analysed and processed. Report is then sent to the competent authority, the National Medicines Agency.

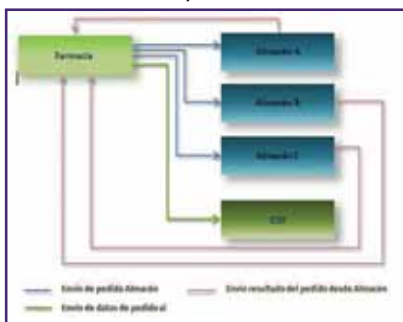
4. **Content of information system:**

Information contained in the system is: the national product number; the number of units of each medicine within an order that has not been supplied to a pharmacy; name of wholesalers that have not been able to serve the orders; any other information about the activity of the pharmacy.

5. **Governance:** CISMED is an

information system set up by community pharmacists that allows to detect in real time general situations of supply disruptions based on the reports from community pharmacies. It provides information to the Spanish supply chain actors and health authorities on availability of medicines in pharmacies and allows pharmacists to know about potential supply disruptions and provide timely solutions to patients and ensure continuity of treatment.

6. **Outline of the process:**



B. Government-led system examples

Belgium

1. **Detection and assessment of medicine shortage:** In line with EU legislation, MAHs are legally obliged to notify all shortages lasting for at least 2 weeks no later than the first week of the shortage. Since July 2016, the legislation has been modified in a way that a temporary stop of

commercialisation of a medicine needs to be notified at least 2 months in advance to the Federal Agency for Medicines and Health Products (FAMHP). The legislative modification contains exceptions to the obligation of notification in cases where notification beforehand is not possible. The stock breaches still need to be notified as soon as possible. Additionally, other Supply Chain Actors (pharmacies, wholesaler-distributors, etc.) can notify the Agency of (potential) shortages. On the basis of these notifications, the Agency will check with the MAH whether or not it consists of a real out of stock, and if yes, will request the company to complete a formal notification. All notified shortages are published on the Agency's website. For those shortages that hold an immediate risk for public health, substitution possibilities are also published. In the case where the company received an MA derogation and is allowed to import a batch of the medicine destined for another Member State, this information is made available on the website.

2. **Information source:** All Supply Chain Actors can notify the Agency of potential medicine shortages.

3. **Level of access:** All Supply Chain Actors have access to the data on the medicines shortages system. The list of medicine shortages is publicly available.

4. **Content of information system:** The published list of shortages contains the following information: human or veterinary medicines; product name; pharmaceutical form; pack size; national product code; beginning date of a shortage; expected date of return to the stock; and reason(s) of the shortage. The information is made available on notifications (daily update) and remains visible until the end of the out-of-stock period is confirmed by the MAH.

5. **Governance:** In Belgium, the federal medicines agency (Federaal Agentschap voor Geneesmiddelen en

Gezondheidsproducten FAMHP/L'Agence Fédérale des Médicaments et des Produits de Santé) publishes on a daily basis a list of medicines experiencing shortages which is established on the basis of information received from MAHs. The notifications and publication are managed by the Agency and the set-up and general policy is guided through a Supply Chain Actors platform "medicines (un)availability".

Portugal

Reports on shortages of medicines to Infarmed are governed by legislation and follows the pathways below:

- a) Information is submitted by the pharmaceutical manufacturers through an online application designed specifically for this purpose ("Shortages Notification System") and is available on www.infarmed.pt
- b) Information can be submitted by other supply chain operators and healthcare professionals – in a two-step approach. Doctors and/or patients are considered as sources of information for the purpose of reporting a medicine shortage. However, the report of the shortage is made in a second step by the manufacturer, in the same way as above, after confirming stock levels with wholesale distributors.

Italy

Since 2014, a full list of products not available due to supply disruption is available on the Italian Medicines Agency (AIFA) website and updated weekly and provided by MAHs.

AIFA, the Ministry of Health, the Regions and the interested stakeholders are working together on a pilot project that sets up a monitoring system for products not available for non-regulatory reasons (for instance parallel trade): to check the presence of the products in the internal market.

Germany

German authorities (Federal Institute for Drugs and Medical Devices,

Paul-Ehrlich-Institut) publish data that is voluntarily provided by pharmaceutical companies. Additional reporting obligations are currently under discussion in a draft legislation as follow up from the "Pharmadialog".

EU level

In November 2013, the EMA established a public catalogue for supply shortages of medicines that have been assessed by the Agency to affect more than one Member State, and for which recommendations have been provided. The aim of the catalogue is to offer stakeholders, healthcare professionals and patients updated information on the reason, the status and the extent of the shortage, while also providing material on relevant related website links and documents. The information is public.

Annex 2: European Union legal framework

MAHs' obligations, as laid down in Directive 2001/83 as amended:

Article 23a: 'If the product ceases to be placed on the market of a Member State, either temporarily or permanently, the marketing authorisation holder shall notify the competent authority of that Member State. Such notification shall, other than in exceptional circumstances, be made no less

than two months before the interruption in the placing on the market of the product. The marketing authorisation holder shall inform the competent authority of the reasons for such action in accordance with Article 123(2).'

Article 81: 'The holder of a marketing authorisation for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered.'

Article 123(2): 'The marketing authorisation holder shall be obliged to notify Member States forthwith of any action taken by him to suspend the marketing of a medicinal product, to withdraw a medicinal product from the market, to request the withdrawal of a marketing authorisation or not to apply for the renewal of a marketing authorisation, together with the reasons for such action. The marketing authorisation holder shall in particular declare if such action is linked to any of the grounds set out in Articles 116 and 117. In such cases, Member States shall ensure that this information is brought to the attention of the Agency.'

MAH obligations, as laid down in Directive 2003/94:

Article 13: 'The manufacturer shall inform the competent authority of any defect that could result in a recall or abnormal restriction on supply and, in so far as is possible, indicate the countries of destination.'

Under the auspices of the work led by EMA, industry trade associations including the EFPIA, Medicines for Europe, the AESGP and the Plasma Protein Therapeutics Association have developed a set of communication principles in order to streamline in a harmonised and risk proportionate framework the diversity in data packages and expectations from the 28 EU Member States' competent authorities and the EMA¹³. This framework encompasses the following elements:

- An identical trigger point for notification based on an agreed definition of a meaningful disruption, and a triaging process based on an evaluation of the level of risk associated with a potential supply chain disruption;
- A harmonised reporting content;
- An agreed time point and recipient of the information for all nationally and centrally approved products.

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WHAT BREXIT MEANS FOR BRITISH QUALIFIED PERSONS

by Malcolm E Brown

I have interviewed a number of British senior pharmacists who were also qualified persons (QPs). This article reports their opinion. All thought that the situation was complex and uncertain.

Malcolm E Brown, PhD, MRPharmS, is a retired pharmacist with over 100 publications. He has worked as production manager (big Pharma), in senior positions in the British National Health Service and as director and consultant. Several licences, for human and veterinary medicines and investigational medicinal products, named him as qualified person.

Threats or weaknesses

Brexit poses several threats or weaknesses. One is pivotal. A hard Brexit would mean that British QPs could no longer certify batches for export to countries that remained inside the European Union (EU). Batches include marketed medicine, investigational medicinal products and active pharmaceutical ingredients. It would be as if the UK QP did not exist in Europe. That is a real worry.

Similarly, the UK would be unable to import batches from EU countries that had already been released in the EU, without further quality control (QC) testing. This would mean repeating testing; costs would increase, so would time. This might cause delays and supply shortages, which could adversely affect patient care.

British QPs would not be recognised for clinical trials in countries remaining in the EU. Companies from the old Eastern Block may offer a cheaper service.

Annex 16 requires that the QP is responsible for the entire supply chain. This includes source material, manufacture, release and storage. This is practicable in large companies. There, a number of QPs may cooperate. However, in small companies, where one QP is responsible for everything, that QP's duties would become more

burdensome. How cooperation between QPs inside and outside the UK can occur cannot be seen.

At this stage, it is difficult to envisage how cooperation between QPs inside and outside the UK would occur to allow smooth progress of commercial authorisation for products manufactured in mainland EU. As QP duties are becoming more and more burdensome, added barriers post-Brexit could reduce the number of QPs prepared to undertake product release duties. Also, there is a risk that potential pharmacist QPs could be put off qualification or practising by any significant increase in requirements.

There is a related concern. Would the British government continue to recognise certain QPs? They are the non-British QPs presently practising in the UK. If not recognised, the number of available QPs in the UK would reduce. Most members listed as eligible to be nominated as QPs on the register of the Royal Pharmaceutical Society are under the transitional regulations. They are at or near the end of their careers.

The European Medicines Agency may relocate from the UK. However, that would not be before 2019.

The existing system may fall apart. The National Health Service (NHS) only funds pharmacies for the cost of, broadly, parallel imports. If

these were unavailable, prescription costs would increase substantially.

Advantages

Brexit does offer advantages. British QPs would have more work. There are three reasons. There would be extra QC testing, more staff would be required in the Medicines and Healthcare Products Regulatory Agency (MHRA) and the requirement for more attendance in working parties and QP groups.

Theoretically, making changes should become quicker and easier. The reason is that the requirement to consult and agree with the EU would vanish.

Messages for government

Governments are urged to change as little as possible.

The government should start talking to industry now. That discussion should involve not just large but also medium-sized and small companies. Government should ensure that the Falsified Medicines Directive 2016/161 is applied. Otherwise, Britons would receive less protection than EU citizens would.

Messages for the Royal Pharmaceutical Society

Frustration was felt that the professional and membership body did not appear to be acting proactively. The General Pharmaceutical Council (GPhC) is a different organisation and the QP does not need to be registered with the GPhC.

If the Society need to increase their membership, they should be more proactive in their person power planning for each of the pharmaceutical sectors, as there are significant opportunities for pharmacists working in the healthcare industries and hospital, opportunities that are currently being filled by other life science graduates. The Society could, for example, facilitate the relocation of pharmacists to other sectors, such as QPs responsible for manufacture of investigational medicine, or information pharmacists, as pharmacists do not need the longer and more expensive course



required for the training of chemists and biologists.

The new role of QPs for pharmacovigilance (QPPV) is expanding. The Society should offer more continuing professional development for industrial pharmacists. There is a substantial amount for community and hospital pharmacists; there is virtually none for industrial pharmacists.

To what extent has the Society lobbied to communicate QP views regarding implications of Brexit? Communicate with pharmacists, healthcare professional groups, the Association of the British Pharmaceutical Industry, the MHRA, regulators, the Department of Health/NHS and government about possible impacts of all aspects of

pharmacy. Do not forget that pharmacy covers development, manufacturing and supply of medicines as well as clinical and dispensing activities. It is important that this happens before the formal negotiations begin, so that we may properly inform those leading Brexit negotiations.

In France, only pharmacists can be QPs. Also, in the French pharmaceutical industry, the *Pharmacien Responsable* (PR) role (including the QPPV function) is central. The role of the PR QP is wide. It includes manufacturing; advertising; medical information; training in medical, drug, claims, monitoring and batch recalls; distribution and storage of products; import; export; marketing

authorisation for the market; labelling; and transport conditions. The PR QP is a French, and not an EU-wide, role. However, Brexit could be a splendid opportunity to consider introducing the QPPV role for British pharmacists.

Overview

A positive perspective has been attempted. However, there is more anxiety than enthusiasm about the impact of Brexit upon QPs.

Little is known about what is going on. Brexit would probably have substantial implications upon QPs. It is suspected that the increased costs and reduced availability of medicines for British patients has not been thought through.

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Compatibilité des injectables avec les matériaux en contact : analyse de risque et stratégie

Commission SFSTP, N. Sehnaï

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Compatibility of materials in contact with parenteral preparations: risk analysis and strategy

Les études de compatibilité entre les matériaux en contact et les produits pharmaceutiques injectables ont pour objectif de démontrer l'absence d'altération de la qualité du produit fini due à une incompatibilité en cours de fabrication ou de conservation du médicament. Dans cette étude, nous avons souhaité aborder le cas le plus critique, celui des formes à usage parentéral, en proposant des éléments d'information et de méthodes afin de réaliser les études pertinentes susceptibles de répondre aux exigences réglementaires, d'anticiper d'éventuelles interactions ou encore d'élucider certains défauts de qualité. Dans une partie introductive, la spécificité de la voie parentérale est rappelée ainsi que les risques toxiques associés à ce mode d'administration. Sont ensuite présentés les matériaux les plus couramment utilisés constituant les équipements de fabrication et conditionnements primaires potentiellement en contact avec le médicament. Un éclairage réglementaire montre que de nombreux textes concernent directement ou indirectement les études de compatibilité. Les deux textes spécifiques aux conditionnements du médicament (FDA et EMA) sont résumés et comparés. La méthodologie proposée ensuite insiste sur l'importance de l'analyse de risque initiale et décrit les principaux facteurs à prendre en compte dans cette démarche. Les résultats de cette analyse permettent la mise en œuvre d'études appropriées, lesquelles, s'il s'agit d'études d'interactions, conduiront à l'obtention de profil d'extractibles et relargables. Dans la mesure où l'impact toxique de ces profils doit être maîtrisé par l'industriel, une partie importante de l'article a été consacrée à l'évaluation toxicologique, tant sur le plan des tests à réaliser que sur les interprétations des résultats des études. À ce stade, des limites acceptables basées sur la documentation disponible sur les matériaux (caractéristiques et toxicité) et/ou sur les résultats de tests toxicologiques devront être déterminées. Mais en l'absence de ces éléments documentaires ou expérimentaux, des recommandations du PQRI aident l'analyste dans la définition des seuils critiques. La dernière partie s'intéresse à la qualité (analyse et audit) des matériaux et articles utilisés dans la fabrication de chaque lot de produit fini conditionné, les contrôles devant garantir un

Compatibility studies on materials in contact with parenteral preparations are designed to demonstrate the absence of alteration of the quality of the finished product due to incompatibility during manufacture or storage of the medicinal product. In this study, we addressed the worst case, that of parenteral preparations, by proposing information and methods to perform the relevant studies in accordance with regulatory requirements and to anticipate possible interactions or elucidate certain quality defects. The introduction recalls the specificity of the parenteral route and the toxic risks associated with this route of administration. The materials most commonly used, corresponding to manufacturing equipment and primary packaging materials potentially in contact with the medicinal product, are then presented. A regulatory review reveals that many texts directly or indirectly concern compatibility studies. The two texts specific to medicinal product packaging (FDA and EMA) are summarized and compared. The proposed methodology then highlights the importance of the initial risk analysis and describes the main factors to be taken into account in this approach. The results of this analysis guide the choice of appropriate interactions studies, leading to definition of extractables and leachables profiles. As the manufacturer must ensure mastery of the toxic impact of these profiles, a large part of the article is devoted to toxicological assessment, including the tests to be performed and interpretations of the test results. Acceptable limits based on the available documentation concerning the materials (characteristics and toxicity) and/or on the results of toxicological tests must be determined at this stage. However, in the absence of these data or experimental results, PQRI guidelines help the analyst to define critical thresholds. The last part of the article concerns the quality (analysis and audit) of materials and articles used in the manufacture of each batch of packaged finished product, the tests required to ensure a constant level of quality and consequently able to demonstrate any change invalidating the conclusions of the initial risk analysis or the results of compatibility studies.

niveau de qualité constant et par conséquent être en mesure de mettre en évidence tout changement invalidant les conclusions de l'analyse de risque initiale ou encore les résultats des études de compatibilité.

Mots clefs : Compatibilité, Extractibles, Relargables, Injectables, Analyse de risque, Interactions contenant-contenu, Toxicité, Sécurité, Qualité.

Key words: Compatibility, Extractables, Leachables, Injectables, Risk analysis, Container-content interactions, Toxicity, Safety, Quality.

INTRODUCTION

Lors d'une précédente commission nous avons abordé la réglementation [1], la méthodologie et les principes généraux des études d'interactions contenant-contenu [2, 3]. Ces travaux ont mis en évidence la nécessité d'approfondir le cas des médicaments administrés par voie parentérale. En effet, les études de compatibilité entre les matériaux en contact et les produits pharmaceutiques administrés par voie parentérale présentent un enjeu majeur eu égard aux risques potentiels pour le patient.

Si, comme pour les autres voies d'administration, la qualité voire l'efficacité du médicament peuvent être remises en cause, les voies intraveineuse (IV), intramusculaire (IM), sous-cutanée (SC), intradermique (ID) ou encore intra-artérielle (IA) présentent un risque important, en termes de sécurité, lié à l'introduction rapide et totale dans la circulation générale, sans aucune barrière physique ou métabolique, de produits toxiques relargués dans le médicament par des matériaux en contact. D'autres voies d'administration parentérales plus spécifiques, telles que les voies intraoculaire ou intra-articulaire par exemple, impliquent des risques toxicologiques particuliers en relation avec les caractéristiques du « tissu cible ».

Bien qu'il n'existe pas de consensus réglementaire précis sur la façon de conduire les études permettant d'évaluer cette compatibilité, les textes de référence confirment par leur niveau d'exigence plus élevé pour les formes injectables que le risque doit être appréhendé spécifiquement pour ces voies d'administration.

L'objectif du travail de la commission était de dresser un état des lieux des particularités des interactions contenant-contenu, notamment au niveau des études d'extractibles et de relargables, dans la production et la conservation des formes pharmaceutiques parentérales, et d'examiner les principales problématiques soulevées par cette voie d'administration afin d'identifier d'une part les éléments importants à retenir dans l'analyse de risque et d'autre part les différentes études analytiques ou expérimentales nécessaires pour l'évaluation finale de la compatibilité.

La commission s'est également intéressée aux risques spécifiques que peuvent présenter les macromolécules sous formes injectables récemment apparues sur le marché (oligonucléotides, peptides, protéines, polysaccharides, etc.) issues des biotechnologies dont le comportement au regard du contenant

INTRODUCTION

In the context of a previous commission, we examined the regulations [1], methodology and general principles of container-content interaction studies [2, 3]. This work demonstrated the need for a more detailed examination of parenterally administered medicinal products, as compatibility studies between materials in contact with parenterally administered medicinal products constitute a major challenge in view of the potential risks for the patient.

Although, like other routes of administration, the quality or even the efficacy of the medicinal product must be determined, the intravenous (IV), intramuscular (IM), subcutaneous (SC), intradermal (ID) or intraarterial (IA) routes are associated with a high safety risk related to the rapid and total introduction into the general circulation, without any physical or metabolic barrier, of toxic products leached into medicinal product by contact with materials. Other more specific parenteral routes of administration, such as intra-articular or intraocular routes, involve particular toxicological risks related to the characteristics of the target tissue.

Although no precise regulatory consensus has been reached concerning the way in which studies should be conducted to evaluate this compatibility, the stricter requirements for parenteral forms indicated in guidelines confirm that the risk must be assessed in specific ways for these routes of administration.

The objective of the commission's work was to review the specificities of container-content interaction, especially in terms of extractables and leachables studies, in the production and storage of parenteral dosage forms and to examine the main issues raised by this route of administration in order to identify the important elements that must be included in risk analysis and the various analytical or experimental studies necessary for final evaluation of container-content compatibility.

The commission also examined the specific risks related to biotechnology-derived macromolecules present in parenteral preparations and recently released onto the market (oligonucleotides, peptides, proteins, polysaccharides, etc.), whose behaviour in relation to the container raises new questions or even

génère de nouvelles interrogations, voire de nouvelles approches méthodologiques.

II SPÉCIFICITÉ DES FORMES INJECTABLES

La voie parentérale à laquelle appartiennent les produits injectables, désignée ainsi en opposition à la voie entérale correspondant à l'administration via le système digestif, regroupe toutes les formes d'administration par injection : SC, ID, IM, IV, IA mais aussi intrapéritonéale ou intracardiaque. Les formes inhalées, bien qu'étant aussi considérées comme faisant partie des formes parentérales, ne seront pas traitées ici.

La grande particularité de la voie parentérale est que le médicament est administré directement dans le milieu intérieur (derme, sang, muscles...) et présente donc une biodisponibilité de 100 %, contrairement à la voie entérale pour laquelle une biodisponibilité supérieure à 30 % est déjà considérée comme généralement satisfaisante. Si ce pourcentage de biodisponibilité est pris en compte dans la posologie du médicament, il doit aussi l'être au regard des relargables qui se retrouvent ainsi en totalité, et rapidement, introduits dans la circulation générale.

Par comparaison avec la voie entérale, la voie parentérale tend à limiter l'action immédiate des organes de détoxification (foie, reins et dans une moindre mesure poumons) sur le médicament et donc sur les éventuels relargables injectés. Administré par voie entérale, ou *per os* (PO), le médicament et les substances indésirables qui l'accompagnent sont résorbés au niveau de l'intestin grêle dont le flux sanguin, en particulier en période post-prandiale, aboutit à près de 80 % directement au niveau hépatique (figure 1). Cette organisation physiologique permet le stockage des nutriments au niveau du foie (synthèse de glycogène) mais aussi une métabolisation immédiate des substances indésirables étrangères (xénobiotiques), au rang desquelles le médicament et les éventuels relargables. Les hépatocytes vont ainsi métaboliser une part plus ou moins importante du principe actif mais aussi tous les toxiques présents dans le flux sanguin issus de l'intestin. Cet « effet de premier passage hépatique » est réduit, voire très marginal, dans le cas des formes administrées par voie parentérale. Introduit directement dans le flux sanguin en IV, le médicament et ses relargables devront réaliser un tour complet de la circulation générale avant de rencontrer les deux principaux organes de détoxification. Une partie du flux sanguin passera ainsi dans les capillaires et les tissus sans être soumis à l'action du foie ou des reins. L'administration IM ralentit le passage dans le flux sanguin du médicament qui sera résorbé sur une durée de 10 à 30 minutes, favorisant encore plus une diffusion locale des molécules dans les tissus. Dans le cas de l'injection ID ou SC, pour lesquelles la cinétique de diffusion dans le sang est encore plus lente, les molécules injectées peuvent agir localement et largement diffuser dans les tissus avant que l'action du foie ou des reins ne soit significative.

new methodological approaches.

II SPECIFICITY OF PARENTERAL PREPARATIONS

The parenteral route used for administration of parenteral preparations, in contrast with the enteral route corresponding to administration via the gastrointestinal tract, comprises all forms of administration by injection: SC, ID, IM, IV, IA but also intraperitoneal or intracardiac. Inhaled forms (OINDP), although also considered to be parenteral preparations, will not be discussed here.

The most characteristic feature of the parenteral route is that the medicinal product is administered directly into the internal environment (dermis, blood, muscles, etc.) and therefore presents a bioavailability of 100 %, unlike the enteral route for which a bioavailability greater than 30 % is generally considered to be satisfactory. Although this percentage bioavailability is taken into account in the dosage of the medicinal product, it must also be taken into account in relation to leachables, all of which are rapidly introduced into the general circulation.

Compared to the enteral route, the parenteral route tends to limit the immediate action of detoxification organs (liver, kidneys and, to a lesser degree, lungs) on the medicinal product and therefore on any leachables injected with the medicinal product. When administered via the enteral route, or *per os* (PO), the medicinal product and any accompanying unwanted substances are absorbed by the small intestine, 80 % of whose blood flow, particularly during the postprandial period, directly enters the liver (Figure 1). This physiological organization allows the storage of nutrients in the liver (glycogen synthesis), but also immediate metabolism of unwanted foreign substances (xenobiotics), including medicinal products and any leachables. Hepatocytes therefore metabolize a variable proportion of the drug substance as well as any toxins present in the blood flow derived from the intestine. This hepatic first-pass effect is reduced, or even very marginal, in the case of parenteral preparations. The medicinal product and its leachables, introduced directly into the bloodflow by IV injection, must complete a full circuit of the general circulation before reaching the two main organs of detoxification. Part of the blood flow therefore circulates through the capillaries and tissues without being submitted to the action of the liver or the kidneys. IM administration slows passage of the medicinal product into the circulation, as it is absorbed over an interval of 10 to 30 minutes, thereby promoting local diffusion of the molecule in the tissues. In the case of ID or SC injection, for which the kinetics of diffusion in the circulation are even slower, injected molecules can act locally and can widely diffuse in the tissues before any significant action of the liver or kidneys.

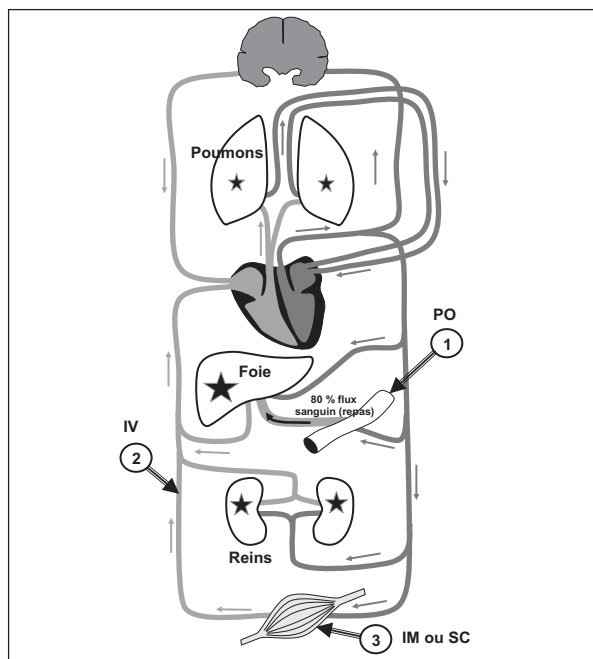


Figure 1. Schéma d'organisation générale de la circulation sanguine indiquant les principaux organes de détoxification (★) et des voies d'administration entérale (1) ou parentérales (2 et 3). PO : per os, IV : intraveineuse, IM : intramusculaire, SC : sous-cutanée.

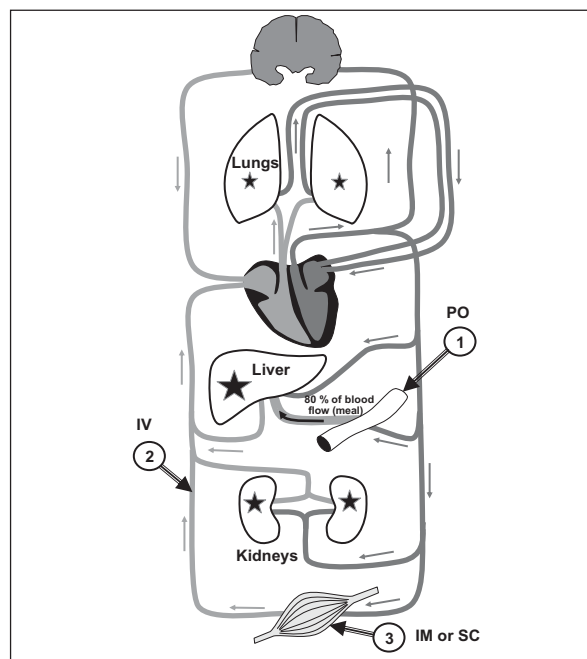


Figure 1. Diagram of the general organization of the blood circulation indicating the main organs of detoxification (★) and the enteral (1) or parenteral (2 and 3) routes of administration. PO: per os, IV: intravenous, IM: intramuscular, SC: subcutaneous.

Il en résulte que si, contrairement à la voie entérale, la voie parentérale permet un dosage très précis du médicament, elle expose l'organisme directement aux effets toxiques potentiels de molécules telles que les relargables.

Certaines voies parentérales (injection intra-oculaire et intra-articulaire) nécessitent des tests spécifiques, comme par exemple compatibilité avec des cellules nerveuses ou la matrice des cartilages (hyaluronanes, protéoglycanes).

III MATÉRIAUX EN CONTACT AVEC LE MÉDICAMENT INJECTABLE

L'interaction du conditionnement primaire, et dans certains cas secondaire, ainsi que les équipements de production en contact direct avec le médicament ou les intermédiaires de fabrication est à prendre en compte dans l'évaluation du risque pour le patient.

Cette évaluation nécessite la connaissance des matériaux, leurs caractéristiques physiques, leur composition et leur compatibilité avec le médicament injectable.

1. CONDITIONNEMENTS ET ÉQUIPEMENTS DE FABRICATION

1.1. Conditionnements primaires et secondaires

On considère comme contenant primaire tout matériau en contact direct avec la solution. Cependant, font partie du conditionnement primaire certains supports d'identification (encre, étiquettes, colles)

Consequently, although, in contrast with the enteral route, the parenteral route allows very precise dosage of the medicinal product, it also directly exposes the body to the potential toxic effects of molecules such as leachables.

Some parenteral routes (intra-articular and intraocular injections) require specific tests such as compatibility tests with nerve cells or cartilage matrix (hyaluronans, proteoglycans, etc.).

III MATERIALS IN CONTACT WITH PARENTERAL PREPARATIONS

The interaction of the primary packaging, and in some cases the secondary packaging, as well as manufacturing equipment in direct contact with the medicinal product or manufacturing intermediates must be taken into account in assessment of the patient risk.

This assessment requires knowledge of the materials, their physical characteristics, their composition and their compatibility with the parenteral preparation.

1. PACKAGING AND MANUFACTURING EQUIPMENT

1.1. Primary and secondary packagings

The primary container is considered to be any material in direct contact with the solution. However, the primary packaging also comprises certain identification supports (ink, labels, glues) that can

susceptibles de migrer dans le produit au travers du contenant, tels que les matériaux polymères.

On considère comme contenant secondaire les matériaux en contact indirect avec le produit (fiche d'information, absorbeur d'humidité, cartonnage, film de suremballage...). Les études d'interaction ne concernent pas les conditionnements secondaires.

La plupart des systèmes de conditionnement pour injectables contiennent des parties en contact direct et indirect avec le médicament. Le *tableau 1* présente les systèmes classiques d'injection. D'autres dispositifs complexes sont également disponibles sur le marché. Dans ce cas, une évaluation de tous les matériaux en contact direct ou non est à réaliser afin d'en tenir compte lors de l'analyse de risque décrite au chapitre IV.

1.2. Équipements de fabrication

Les équipements et matériaux en contact avec le médicament en cours de fabrication peuvent être très variés : tuyaux de transfert, joints, filtres, poches plastique de conditionnement intermédiaire, cuves inox... et font l'objet d'une attention particulière dans le cas des produits injectables, notamment pour les matériaux en contact avec les substances actives ou le produit final [4]. Certains procédés, notamment pour les produits de biotechnologie, sont complexes car faisant intervenir de nombreux matériaux.

Cependant, bien que les procédés de fabrication

migrate into the product through the container, such as polymer materials.

The secondary container is considered to be any material in indirect contact with the product (package leaflet, desiccant, outer pack, overwrap film, etc.). Interaction studies do not concern secondary packaging.

Most packaging systems for parenteral preparations comprise parts in indirect and direct contact with the medicinal product. *Table 1* presents the classical injection devices. Other complex devices are also available on the market, in which case, evaluation of all materials in direct or indirect contact with the medicinal product must be taken into account during the risk analysis described in Chapter IV.

1.2. Manufacturing equipment

Various equipment and materials can be in contact with the medicinal product during manufacture: transfer tubing, seals, filters, intermediate packaging plastic bags, stainless steel tanks, etc. and are subject to particular attention in the case of parenteral preparations especially for materials in contact with drug substances or the finished product [4]. Some manufacturing processes, especially for biotechnology products, are particularly complex, as they involve a large number of materials.

However, although the manufacturing process and

Tableau 1. Les systèmes de conditionnement pour injectables.

Table 1. Packaging systems for parenteral preparations.

Système d'emballage Packaging system	Composants Components	Contact indirect (I) ou direct (D) Indirect (I) or direct contact (D)
Système poche Bag system	Film primaire (multicouche, PVC, PP...)/Primary film (multilayer, PVC, PP, etc.) Port d'injection (PP...) avec bouchon (élastomère)/Injection port (PP, etc.) with stopper (elastomer) Système de sertissage (cap)/Crimping system (cap) Encres/Ink Optionnel : suremballage, absorbeur et indicateur d'oxygène/Optional: overwrap; oxygen scavenger and oxygen indicator	D D I I I
Flacon/vial Bottle/vial	Flacon en plastique (PE, PP...) ou verre/Plastic (PE, PP, etc.) or glass bottle Bouchon (élastomère)/Stopper (elastomer) Encre (impression direct sur le flacon) ou étiquette avec colle et encre/Ink (direct printing on the bottle) or label with glue and ink Système de sertissage (cap)/Crimping system (cap)	D D I I
Seringue Syringe	Seringue en verre ou plastique (PP...)/Plastic (PP, etc.) or glass syringe Piston/Plunger Joint/Seal Lubrifiant/Lubricant Aiguille/Needle Protège-aiguille et protège-embout, dispositif de sécurité/Needle cover and tip cover, safety device Colle/Glue Encre (impression direct sur la seringue) ou étiquette avec colle et encre/Ink (direct printing on the cartridge) or label with glue and ink	D D D D I I I
Cartouche Cartridge	Cartouche en verre ou plastique (PP...)/Plastic (PP, etc.) or glass cartridge Piston/Plunger Joint/Seal Lubrifiant/Lubricant Colle/Glue Encre (impression direct sur la cartouche) ou étiquette avec colle et encre/Ink (direct printing on the cartridge) or label with glue and ink	D D D D I I
Ampoule	Ampoule en plastique (PE, PP...) ou verre/Plastic (PE, PP, etc.) or glass ampoule Encre (impression direct sur l'ampoule) ou étiquette avec colle et encre/Ink (direct printing on the ampoule) or label with glue and ink	D I

des médicaments injectables et les matériaux utilisés soient très différents les uns des autres, il est possible d'appliquer la démarche et l'analyse de risque proposées dans cet article.

2. PRÉREQUIS ET COMPOSITION DES MATÉRIEAUX EN CONTACT

Les matériaux répertoriés dans cette partie sont utilisés pour le conditionnement mais peuvent également constituer un matériel ou équipement de fabrication.

Les caractéristiques de ces matériaux sont disponibles et fournies par le fabricant avec un niveau de détails très variable. La composition est souvent confidentielle et il appartient à l'exploitant du médicament d'entretenir une relation de confiance avec les fournisseurs pour obtenir les informations dont il aura besoin soit pour répondre aux exigences réglementaires (information à fournir aux autorités), soit pour effectuer des études en laboratoire (études d'extractibles et relargables par exemple). Dans le cas des matériaux plastiques, le fournisseur de matière première peut être différent du fournisseur de produit fini (film, bouteille...) appelé « transformateur » ; en effet, celui-ci met en forme ou assemble les éléments des matériaux en contact en ajoutant des adjuvants et en transformant la matière première.

La qualification des matériaux (ou qualification initiale) est une étape importante du développement, comme il est rappelé dans le chapitre IV.1.2. Elle précède l'étude de compatibilité qui, dans le cas des injectables, nécessite la plupart du temps de réaliser une recherche de produits issus du matériau et relargués dans le médicament. Il apparaît donc que la connaissance de la composition précise des matériaux est un élément essentiel.

Les produits relargués retrouvés dans le produit fini ne sont pas nécessairement issus du contenant primaire mais peuvent provenir des étapes de sa fabrication.

Le *tableau 2* présente une liste non exhaustive des matériaux pouvant être en contact avec le produit au cours du procédé de fabrication. La nature de ces matériaux devra être prise en compte dans l'analyse de risque.

2.1. Verre

La composition du verre de type I est décrite dans le *tableau 3*. Les exigences pour les récipients en verre à usage pharmaceutique sont décrites dans la Ph. Eur. 3.2.1 et l'USP <661>.

Tableau 2. Matériaux pouvant être en contact avec le produit au cours du procédé de fabrication.
Table 2. Materials possibly in contact with the product during the manufacturing process.

Équipement/Equipment	Type de matériaux/Type of materials
Cuves de stockage/de transport Storage/transport tanks Tuyaux de transfert/Transfer tubing Filtres/Filters Aiguilles de répartition/Filling nozzles Joints/Seals	Acier inox, verre, plastique (PE, EVA en général)... Stainless steel, glass, plastic (generally PE, EVA), etc. PP, silicone, PVC, EVA... Verre, polymère.../Glass, polymer, etc. Acier inox/Stainless steel Elastomères, PP, silicone...

the materials used for parenteral preparations differ considerably from one product to another, the same approach and risk analysis proposed in this article can be applied.

2. PREREQUISITES AND COMPOSITION OF CONTACT MATERIALS

The materials described in this section are used for packaging, but can also constitute manufacturing materials or equipment.

The characteristics of these materials are available and provided by the manufacturer with very variable degrees of detail. The composition is often confidential and it is the responsibility of the applicant to maintain a relationship of confidence with suppliers in order to obtain the information they need to meet regulatory requirements (information to be provided to authorities) or to conduct laboratory studies (for example, studies of extractables and leachables). The supplier of the starting materials of plastic materials may be different from the transformer of plastic materials (film, bottles, etc.), who manufactures or assembles materials in contact with the medicinal product by adding adjuvants and by transforming the starting material.

Qualification of materials (or initial qualification) is an important step of development, as recalled in chapter IV.1.2. It must be performed before compatibility studies, which, in the case of parenteral preparations, usually require screening for substances derived from the material and leached into the medicinal product. Knowledge of the precise composition of the materials therefore appears to be essential.

Leachables detected in the finished product are not necessarily derived from the primary container, but can also be derived from manufacturing steps.

Table 2 presents a non-comprehensive list of materials possibly in contact with the product during the manufacturing process. The nature of these materials must be taken into account in risk analysis.

2.1. Glass

The composition of type I glass is described in *Table 3*. The requirements for glass containers for pharmaceutical use are described in Ph. Eur. 3.2.1 and USP <661>.



Ce verre peut être soumis à des traitements de surface pour améliorer la compatibilité avec le médicament quand celui-ci présente une sensibilité particulière (exemple : eau PPI et revêtement au sulfate d'ammonium).

Tableau 3. Composition du verre de type I.
Table 3. Composition of type I glass.

Components(% w/w) / Type Glass I
SiO ₂ / 72-74
Al ₂ O ₃ / 6-7
Na ₂ O / 6.5-8.5
K ₂ O / 1.0-1.3
CaO / 0.5-1.5
BaO / 0.0- 2.5
MgO / -
B ₂ O ₃ / 10-11

This glass can be submitted to treatment of the surface to improve the compatibility with particularly sensitive medicinal products (e.g.: water for injection and ammonium sulphate coating).

2.2. Polymères plastiques et élastomères

Les polymères sont parmi les matériaux les plus délicats à traiter de par la complexité de leur composition et de leur procédé de fabrication. Ils sont la principale source d'extractibles et de relargables et génèrent une grande variété de molécules.

L'origine de ces extractibles et relargables est multiple :

- résidus de polymérisation : provenant du polymère lui-même (monomères, oligomères), solvants ou tensio-actifs de polymérisation, impuretés non polymérisables, impuretés liées à l'équipement, résidus de catalyseurs, etc. ;
- additifs de fabrication (plastifiants, stabilisateurs, lubrifiants, agents de charge, colorants...) ;
- additifs altérés : produits de réaction ou de terminaison (vulcanisants, anti-oxydants, antiozones...) ;
- composés résultant de réactions avec des additifs (impuretés du polymère, noir de carbone) ;
- produits de dégradation.

La conformité des polymères et élastomères aux différentes pharmacopées permet de s'assurer de la qualité chimique du plastique.

La structure de ces produits est très variable comme on peut le constater dans la Ph. Eur 3.1.13. « Additifs pour plastiques ». Pour l'Europe, les additifs autorisés et limites acceptables dans la matière première plastique pour usage parentéral sont donnés dans les monographies correspondantes. Une liste non exhaustive des composés courants est fournie en annexe 1.

Les flacons ou ampoules sont fabriqués à partir de polymères : polypropylène (PP)-polyéthylène (PE). Les poches sont souvent composées de films multicouches. Les différentes couches sont choisies en fonction des propriétés recherchées. La couche en contact direct avec la solution est généralement composée de polyoléfines (exemple : polypropylène (PP), polyéthylène (PE), copolymère d'éthylène-vinyl acetate (EVA)). Le PP permet un soudage de la poche et résiste à la stérilisation à 121 °C. Le grade pharmaceutique est facilement disponible. La couche externe doit présenter un point de fusion supérieur à la couche interne pour résister à la chaleur. Des polyamides (PA), du polyéthylène téréphtalate (PET), des copolyester-ether ou des homopolymères de PP sont couramment utilisés. L'adhésif entre les couches sera choisi en fonction des films à assembler. Parmi eux, l'anhydride maléique peut être employée. Ces films peuvent contenir des couches intermédiaires dites

2.2. Plastic polymers and elastomers

Polymers are some of the most delicate materials to treat due to the complexity of their composition and their manufacturing process. They are the main source of extractables and leachables and generate a wide range of molecules.

These extractables and leachables have multiple origins:

- polymerization residues: derived from the polymer itself (monomers, oligomers), polymerization solvents or surfactants, non-polymerizable impurities, equipment-related impurities, catalyst residues, etc. ;
- manufacturing additives (plasticisers, stabilisers, lubricants, bulking agents, dyes, etc.);
- altered additives: reaction products or termination-products (vulcanisers, antioxidants, antiozones, etc.);
- compounds resulting from reactions with additives (polymer impurities, carbon black);
- degradation products.

The compliance of polymers and elastomers with the various pharmacopoeias confirms the chemical quality of the plastic.

As illustrated by Ph. Eur 3.1.13 Plastic additives, these products have a very variable structure. The plastic additives authorized in Europe and the acceptable limits in the plastic starting material for parenteral preparations are defined in the corresponding monographs. A non-comprehensive list of common compounds is provided in Appendix 1.

Vials or ampoules are made from polymers: polypropylene (PP)-polyethylene (PE). Bags are often composed of multilayer films. The various layers are chosen on the basis of the desired properties. The layer in direct contact with the solution is generally composed of polyolefines, (e.g.: polypropylene (PP), polyethylene (PE), ethylene vinyl acetate copolymer (EVA)). PP allows welding of the bag and resists sterilization at 121 °C. Pharmaceutical grade PP is readily available. The external layer must present a melting point higher than that of the internal layer to resist heat. Polyamides (PA), polyethylene terephthalate (PET), polypropylene ether copolyesters or homopolymers are commonly used. The adhesive between layers is selected according to the various films to be assembled. Maleic anhydride can be used. These films can contain intermediate, so-called barrier layers to water and/or oxygen: ethylene vinyl alcohol (EVOH), metallisation (for example SiOx).



« barrières » à l'eau et/ou à l'oxygène: éthylène-vinyl alcool (EVOH), métallisation (par exemple SiO_x).

Seule la Pharmacopée japonaise décrit des tests adaptés pour les films mono- ou multi-couches [5].

2.3. Acier inoxydable

L'acier inoxydable peut contenir les éléments tels que : azote, carbone, manganèse, silice, phosphore, soufre, nickel, chrome, molybdène, titane, aluminium, niobium. La composition qualitative et quantitative est décrite dans les normes AISI et ISO.

2.4. Lubrifiants

Les lubrifiants ne sont pas à proprement parler des éléments du contenant primaire mais leur présence est très fréquente et aide à la mise en forme du contenant ou à son fonctionnement (lubrification des pistons dans les seringues)

Certains lubrifiants, telles la diméticone (pureté 99 %) ou l'huile de silicone, sont décrits dans la Ph.Eur. et l'USP/NF. D'autres font l'objet de monographies internes en l'absence de monographies de référence.

Des lubrifiants contenant différentes formes d'éther de polyéthylène glycol sont généralement utilisés dans la lubrification de ressorts et billes de valves (essentiellement pour des formes non parentérales). Une analyse de risque doit être réalisée en cas d'emploi dans des formes à usage parentéral.

2.5. Colles

De nombreuses colles (acrylate, uréthane, polyester, époxydes) sont susceptibles d'intervenir dans la mise en forme finale du contenant (collage des opercules, assemblage aiguille/corps de seringue, étiquettes, etc.).

Même les adhésifs à faible potentiel de migration destinés aux produits pharmaceutiques doivent faire l'objet d'une évaluation, tout particulièrement si, comme l'indique le fabricant, ces adhésifs sont soumis à un traitement de stérilisation.

2.6. Encres

Les modes d'impression influencent les compositions chimiques des encres et par conséquent les profils d'extractibles.

Les impressions couramment utilisées sont :

- impression par transfert thermique (*thermotransfer*) : un film polyester est imprégné d'encre (résine, cire ou cire-résine) ;
- impression jet d'encre (*inkjet*) : l'encre la plus courante est une encre à base de colorant dissous dans un solvant. Les encres à pigments sont aussi utilisées. Elles comportent des particules colorées solides volumineuses (quelques microns), parfois enrobées d'une gaine de résine, qui sont simplement transportées par un fluide transparent et facilement évaporables ;
- impression « *hot stamp* » : c'est un procédé utilisant un ruban en PET couvert d'encre ;

Only the Japanese Pharmacopoeia describes appropriate tests for single-layer or multilayer films [5].

2.3. Stainless steel

Stainless steel can contain various elements such as: nitrogen, carbon, manganese, silica, phosphorus, sulphur, nickel, chromium, molybdenum, titanium, aluminium, niobium. The qualitative and quantitative composition is described in AISI and ISO standards.

2.4. Lubricants

Lubricants are not to strictly speaking primary packaging materials, but they are very frequently present and are used for assembly or functioning of the container (plunger lubrication in syringes).

Certain lubricants, such as dimeticone (99 % purity) or silicone oil are described in Ph. Eur. and USP/NF. Other lubricants are described in in-house monographs in the absence of reference monographs.

Lubricants containing various forms of polyethyleneglycol ether are generally used for the lubrication of springs and ball valves (essentially for non-parenteral preparations). Risk analysis must be performed when these substances are used for parenteral preparations.

2.5. Glues

Many glues (acrylate, urethane, polyester, epoxides) may be used in the final assembly of the container (gluing of caps, needle/syringe body assembly, labels, etc.).

Even adhesives with a low potential for migration used in pharmaceutical products must be submitted to evaluation, especially when the manufacturer indicates that these adhesives are submitted to a sterilization treatment.

2.6. Inks

The type of printing technology influences the chemical composition of the ink and consequently the extractables profiles.

Printing technologies commonly used are:

- thermal transfer printing: a polyester film is impregnated with ink (resin, wax or wax-resin);
- inkjet printing: the ink most commonly used is composed of a dye dissolved in a solvent. Pigment inks are also used. They consist of large (several microns), solid, coloured particles, sometimes coated with a layer of resin, that are simply transported by a transparent and readily evaporated fluid;
- hot stamp printing is a process using an ink-coated PET ribbon;
- flexography: it is a process that uses a flexible relief plate made of a light-sensitive polymer. The ink is

- flexographie : c'est un procédé en relief sur lequel la forme imprimante est un photopolymère flexible. Le séchage des encres se fait par évaporation forcée du ou des solvants lors du passage de l'imprimé dans un four à air chaud ou par radiation ou micro-onde. Il y a alors apport calorifique ; à ne pas confondre avec le séchage ultraviolet qui, lui, implique des changements chimiques de l'encre.

Les composés de l'encre (polymères, pigments, additifs) pouvant migrer à travers le packaging, la formulation devra être conforme aux critères toxicologiques. Ainsi les solvants et les pigments devront être scrupuleusement choisis en fonction de la liste négative des différentes agences (exemple : FDA).

Les solvants contenus dans ces encres ne sont que temporaires car ils sont éliminés par évaporation et/ou infiltration lors du séchage de l'imprimé. De ce fait, ils ne participent théoriquement pas aux propriétés finales du film d'encre. Cependant, il arrive que des solvants résiduels soient prisonniers et il en résulte des problèmes d'odeur, voire de toxicité.

La réglementation ICH sur les solvants résiduels dans les médicaments [6] peut être appliquée. L'utilisation de solvant de classe I sera à éviter et de la classe II à limiter. Les solvants de classe III sont à utiliser dans la mesure du possible.

Une liste de pigments autorisés pour usage pharmaceutique est disponible aux États-Unis [7]. En Europe, une liste pour usage alimentaire est donnée dans deux directives [8, 9].

Les acrylates, souvent utilisés dans les formulations UV *inkjet*, doivent être choisis en fonction de leur toxicité.

3. EXIGENCES RÉGLEMENTAIRES

3.1. Textes fondamentaux

La réglementation couvre les domaines qualité et prérequis pour toute demande d'autorisation de mise sur le marché ou de variation. Elle est particulièrement exigeante pour les produits classés à « haut risque » tels que les produits en solution, suspension, voire les poudres ou lyophilisats à reconstituer et destinés à une administration parentérale.

Les pharmacopées et guides de bonnes pratiques de fabrication s'attachent à encadrer la qualité des matières premières pour fabrication des récipients et les récipients eux-mêmes, la qualification du matériau et ses caractéristiques ainsi que les démarches d'audit des fournisseurs. Les risques d'interaction entre un équipement et le produit fini pendant sa fabrication sont évalués lors de la qualification des matériaux et de la validation du procédé de fabrication.

Les bonnes pratiques de fabrication européennes (EU GMP), américaines (21CFR part 201.65) ou internationales (ICH Q7) précisent que les équipements de production en contact avec le produit ne doivent pas être réactifs, ou relarguer des additifs qui peuvent affecter la qualité finale du produit.

Les *guidelines* régionales pour l'Europe, les États-Unis ou le Japon et les exigences harmonisées

dried by forced evaporation of the solvent or solvents during passage of the imprinted surface in a hot air oven or by radiation or microwaves. This process therefore requires heating, not to be confused with ultraviolet drying, which involves chemical changes of the ink.

As ink compounds (polymers, pigments, additives) are able to migrate across the packaging, the formulation must comply with toxicological criteria. Solvents and pigments must therefore be rigorously selected according to the negative lists established by various agencies (e.g.: FDA).

The solvents contained in these inks are only temporary because they are eliminated by evaporation and/or infiltration during drying of the imprinted surface. Consequently, they theoretically do not participate in the final properties of the ink film. However, residual solvents are sometimes trapped in the ink, resulting in an unpleasant odour or even toxicity.

ICH guidelines on residual solvents in medicinal products [6] can be applied. The use of Class I solvents should be avoided and the use of Class II solvents should be limited. Class III solvents should be used as far as possible.

A list of pigments authorised for pharmaceutical use is available in the USA [7]. In Europe, a list of pigments for use in foodstuffs has been defined in two directives [8, 9].

Acrylates, often used in UV inkjet formulations, must be selected according to their toxicity.

3. REGULATORY REQUIREMENTS

3.1. Main regulatory guidelines

Legislation defines the quality criteria and prerequisites for all marketing authorisation applications or variations. It is particularly strict for "high-risk" products such as solutions, suspensions or even powders or freeze-dried powders to be reconstituted and intended for parenteral administration.

The pharmacopoeias and good manufacturing practice guidelines define the quality of starting materials for the manufacture of containers and the containers themselves, equipment qualification and equipment characteristics as well as supplier audit approaches. The risks of interactions between equipment and the finished product during manufacture are evaluated during equipment qualification and manufacturing process validation.

European (EU GMP), US (21CFR Part 201.65) or International (ICH Q7) good manufacturing practice guidelines specify that production equipment in contact with the product must not be reactive or release additives that could affect the final quality of the product.

Regional guidelines for Europe, USA or Japan and harmonized requirements for these three regions

pour ces trois régions (ICH) définissent les tests de développement à réaliser pour justifier le choix du conditionnement et établir les spécifications selon l'usage ainsi que celles du produit fini.

Deux textes fondamentaux de référence, l'un applicable en Europe [10], l'autre aux États-Unis [11], décrivent selon les risques (forme physique et voie d'administration) les informations à fournir et les études à réaliser. Le texte EMA concerne uniquement les matériaux plastiques excluant les élastomères alors que le texte FDA est plus général et inclut également les contenants en verre. De plus, l'approche qualité est particulièrement bien détaillée dans ce dernier document.

Le *tableau 4* résume les exigences répertoriées dans les deux documents pour les injectables. La place des informations à fournir lors d'une soumission selon les sections du CTD est clairement identifiée dans le document européen alors qu'elle ne l'est pas dans le document de la FDA, car il est antérieur à la définition des sections du CTD. Cependant, nous indiquons dans le *tableau 4* la place supposée des informations demandées par la FDA.

Si des essais de compatibilité avec les dispositifs d'administration sont nécessaires, ils pourront être introduits dans la partie 3.2.P2.4.

Bien que l'organisation des chapitres de ces textes soit différente, ainsi que le montre le *tableau 4*, les exigences sont similaires et distinguent :

- l'étape de développement où seront réalisées la qualification initiale du conditionnement et ses composants ainsi que les études d'extractibles et de relargables, qui permettent de justifier du choix des matériaux et système de conditionnement (primaire, voire secondaire),
- l'étape de définition des contrôles de routine ou périodiques qui seront effectués après approbation du médicament afin de garantir la continuité des caractéristiques établies lors de la qualification initiale et des études de compatibilité.

L'évaluation du risque d'interaction avec les équipements mis en œuvre lors de la fabrication du médicament devra être fournie dans la partie 3.2.P2.3 « Manufacturing process development », en particulier celles qui concernent la compatibilité des filtres, en réponse aux exigences sur la validation du procédé et sur la justification des contrôles *in-process*.

Les textes fondamentaux doivent aujourd'hui être considérés au regard du concept de *quality by design* introduit par les *guidelines* ICH Q8, Q9 pour les produits nouveaux. Ceux-ci confirment entre autres que les études réalisées sur tout le processus de fabrication et les variations acceptables des paramètres critiques, et non plus uniquement sur le produit fini lui-même, permettent de limiter les risques de défaut de qualité.

3.2. Les guides et supports techniques

Les textes fondamentaux suscitent parfois des difficultés d'interprétation. De plus, les limites, les essais et les niveaux de risque acceptables ne sont pas définis par la réglementation. C'est la raison pour

(ICH) define the development tests that must be performed to justify the choice of packaging and to establish specifications according to the use and the specifications of the finished product.

Two regulations, one applicable in Europe [10] and the other applicable in the United States [11], describe the information to be provided and the tests to be performed according to the risks (physical form and route of administration). The EMA text exclusively concerns plastic materials, excluding elastomers, while the FDA text is more general and also concerns glass containers. The quality approach is also described in particular detail in the FDA document.

Table 4 summarises the requirements defined for parenteral preparations in these two documents. The location of documentation to be provided in marketing authorisation applications according to the sections of the CTD is clearly identified in the European document, but not in the FDA document, which was published prior to definition of the sections of the CTD. However, *Table 4* indicates the supposed location of the documentation required by FDA.

When compatibility tests with administration devices are required, they can be described in section 3.2.P2.4.

Although the organization of the chapters of these texts differ, as shown in *Table 4*, the requirements are similar and distinguish:

- the development step, which must comprise initial qualification of the packaging and its components as well as extractables and leachables studies in order to justify the choice of materials and the packaging system (primary or even secondary);
- the step of definition of routine or periodic control tests, that are performed after approval of the medicinal product in order to ensure continuity of the characteristics established at the time of initial qualification and compatibility studies.

Evaluation of the risk of interaction with the equipment used during manufacture of the medicinal product must be provided in section 3.2.P2.3 "Manufacturing process development", particularly studies concerning compatibility of filters, in response to process validation and justification of in-process control test requirements.

These regulations must now be considered in the light of the quality by design concept, introduced by guidelines ICH Q8, Q9 for new products. Among other things, these guidelines confirm that the studies performed on the entire manufacturing process and acceptable variations of critical parameters and no longer exclusively on the finished product limit the risks of quality defects.

3.2. Guidelines and technical documents

Regulations can sometimes be difficult to interpret and they also do not define limits, tests and acceptable risk levels, which is why guidelines have been proposed by pharmaceutical manufacturing

Tableau 4. Textes fondamentaux EMA et FDA. Exigences pour les formes injectables.

	EMA [10]	FDA [11]
Champ d'application	Conditionnement primaire et conditionnement secondaire présentant un risque de migration (encres et colles). Principe actif (PA) en vrac et produit fini (PF) conditionné	
	Conditionnement plastique	Tout matériau, concerne de plus, les PF en vrac
Objectifs	Documentation pour un enregistrement (AMM)	
	ou variation	DMF type III (conditionnement) et II (matériau du conditionnement). Opérations de reconditionnement
Références réglementaires	Stabilité (ICH, EMA for existing product), development pharmaceuticals (EMA), Ph.Eur (voir chapitre 10), dir. eur. relatives aux matériaux plastiques en contact avec les denrées alimentaires	21 et 16 CFR, (control, packaging, indirect food additives, production, special packaging, parenteral DP in plastic...), Stabilité (ICH), guidelines pour essais cliniques USP (voir chapitre 10)
Exigences pour les injectables (Produit fini)		
Forme	Non solide, voie parentérale	Injectables liquide ou suspension, poudre pour injection
Pharmaceutical development (3.2.P.2.4)	<p>Compatibilité</p> <p>- Extraction /conditions de stress : solvant approprié (simulation, placebo). Pour matériau non pharmacopéé ou additifs en qualité et quantité à définir de par le choix laissé par la monographie pharmacopéé.</p> <p>- Interaction (forme solide lyophilisat si nécessaire et forme liquide) :</p> <ul style="list-style-type: none"> • migration (relargables)/conditions normales PF, placebo, simulation : évaluer l'impact sur l'efficacité, la stabilité et la toxicité. <p>Méthodes générales pharmacopéé ou validées. Proposer des valeurs limites max de relargables ou démontrer par calcul que le max relargué est non toxique. Démontrer l'absence d'encres et de colles. Justifier l'absence de cette étude</p> <ul style="list-style-type: none"> • étude de sorption (perte de quantité) : si changement en cours de stabilité <p>Photostabilité</p> <p>Impact sur la compatibilité entre conditionnement et forme pharmaceutique en cas de dégradation du matériau à la lumière</p> <p>Influence des étapes de fabrication sur le conditionnement (stérilisation)</p>	<p>« Suitability » Adéquation conditionnement et ses composants</p> <p>- Protection (gaz, lumière, étanchéité, contamination microbienne)</p> <p>- « Compatibility » (lors de la qualification des matériaux et du conditionnement ou en stabilité)</p> <ul style="list-style-type: none"> • perte de titre, diminution d'un excipient : adsorption, absorption • dégradation du PA ou d'un excipient induit par les produits relargués • précipitation due au changement de pH • décoloration du PF ou du conditionnement • fragilité du conditionnement <p>- « Safety » (1) → extractibles/relargables/données toxicologiques</p> <ul style="list-style-type: none"> • étude de la toxicité des produits potentiellement relargués dans le PF. Milieux appropriés (PF, placebo...) • évaluation de la toxicité des extractibles avec les tests biologiques USP <87> <88> pour les plastiques et USP<381> pour les fermetures en élastomère <p>- Performance (fonctionnalité, dispensation)</p>
Container/ closure system (3.2.P.7)	<p>Description matériau(x) et conditionnement</p> <p>Nom du/des fournisseur(s), composition qualitative complète du matériau si non décrit à la Ph.Eur. ou si la Ph.Eur. autorise plusieurs additifs au choix ou plusieurs limites.</p> <p>Spécifications :</p> <ul style="list-style-type: none"> • réf. Ph.Eur. ou États membres • monographie interne : description, identification matériau, caractéristiques physiques, identification des colorants et additifs susceptibles de migrer, nature et quantité des extractibles <p>Certificat d'analyse : sur un lot représentatif</p>	<p>Description</p> <p>Pour chaque composant du conditionnement primaire : nom matériau, code, fabricant, description physique, traitement (stérilisation)</p> <p>Description du conditionnement secondaire protecteur ou source de contamination</p> <p>Contrôle qualité</p> <p>Pour limiter les variations de qualité après enregistrement</p> <p>Caractéristiques physiques, composition chimique provenant du fabricant du matériau et du transformateur. En cas de changement le fournisseur doit informer l'exploitant. Un programme d'inspection des fournisseurs doit être disponible. L'exploitant peut déléguer l'analyse s'il fait une identification et vérifie périodiquement la validité des résultats du fournisseur. L'information peut être dans le DMF pour les matériaux. On distingue les faibles vol. (< 100 mL) et les larges vol. (> 100 mL)</p> <p>Certificat d'analyse ou certificat de certification</p>
Pharma. dev. (3.2.P.2.4) or Stability (3.2.P.8)	En l'absence d'étude de migration réalisée en cours de développement. L'étude des relargables est faite lors du suivi de stabilité en conditions normales et accélérées.	Stabilité : les études de compatibilité et de sécurité peuvent être faites pendant l'étude de stabilité selon des conditions ICH
Données toxicologiques (2)	Pour les extractibles et relargables, selon leur quantité et structure chimique même s'ils sont approuvés dans la réglementation alimentaire sauf s'ils sont décrits dans une pharmacopéé.	« Safety » : évaluation toxicologique (tests ou littérature) suite aux études de relargables

(1) La partie « safety » comprend les études de relargables en vue de leur évaluation toxicologique. (2) Les données de la littérature et les résultats des essais seraient à fournir dans le Mod. 2 sect. 2.6.6.8, Mod. 4. sect. 2.3.7.6.

Table 4. EMA and FDA regulations. Requirements for parenteral forms

	EMA [10]	FDA [11]
Scope	Primary packaging and secondary packaging with a risk of migration (ink and pastes). Bulk drug substance (DS) and packaged drug product (DP)	
	Plastic packaging	All material, concerns also bulk DP
Objectives	Marketing authorisation (MA) application or variation documentation	
	or variation	DMF types III (packaging) and II (packaging material). Repackaging operations
Regulatory references	Stability (ICH, EMA for existing product), development pharmaceuticals (EMA), Ph. Eur (see chapter 10), European directives on plastic materials in contact with foodstuffs	21 and 16 CFR, (control, packaging, indirect food additives, production, special packaging, parenteral DP in plastic, etc.), Stability (ICH), USP guidelines for clinical trials (see chapter 10)
Requirements for parenterals (drug product)		
Form	Non-solid, parenteral route	Injectables or suspensions, powder for injection
Pharmaceutical development (3.2.P2.4)	<p>Compatibility</p> <ul style="list-style-type: none"> - Extraction/stress conditions Appropriate solvent (simulation, placebo). For plastic materials or additives not described in a pharmacopoeia, quality and quantity to be defined according to the Pharmacopoeia monograph. - Interaction (solid form, freeze-dried powder if necessary and liquid form). • Migration (leachables) under normal conditions <p>DP, placebo, simulation: evaluate the impact on efficacy, stability and toxicity.</p> <p>General Pharmacopoeia or validated methods. Propose maxim limits for leachables or demonstrate by calculation that the maximum leachable is non-toxic.</p> <p>Demonstrate the absence of inks and glues.</p> <p>Justify the absence of this study.</p> <ul style="list-style-type: none"> • Sorption studies (loss of quantity): if change during stability studies <p>Photostability</p> <p>Impact on container/medicinal product compatibility in the case of degradation of the material caused by light</p> <p>Influence of manufacturing steps on packaging (sterilization)</p>	<p>Suitability of packaging and its components</p> <ul style="list-style-type: none"> - Protection (reactive gases, light, water vapour, microbial contamination) - « Compatibility » (during qualification of materials and packaging or stability studies) • loss of potency, reduction of an excipient: adsorption, absorption • degradation of the DS or an excipient induced by products released • precipitation due to a change of pH • discolouration of the DP or the packaging • fragility of the packaging - « Safety » (1) → extractables/leachables/toxicological data • toxicity study of products potentially released into the DP. Appropriate media (DP, placebo, etc.) • evaluation of the toxicity of extractables by biological reactivity tests USP <87> <88> for plastics and USP <381> for elastomer closures - Performance (functionality, drug delivery)
Container/closure system (3.2.P7)	<p>Description materials and packaging</p> <p>Name of supplier(s), complete qualitative composition of the material if not described in Ph. Eur. or if Ph. Eur. allows the choice of several additives or several limits.</p> <p>Specifications :</p> <ul style="list-style-type: none"> • Ph. Eur or Member States references • in-house monograph: description, material identification, physical characteristics, identification of dyes and additives likely to migrate, nature and quantity of extractables <p>Certificate of analysis : on a representative batch</p>	<p>Description</p> <p>For each packaging component of the primary packaging: material name, code, manufacturer, physical description, treatment (sterilization)</p> <p>Description of the protective secondary packaging or source of contamination</p> <p>Quality control</p> <p>To limit quality variations after approval</p> <p>Physical characteristics, chemical composition obtained from the material manufacturer and packager</p> <p>In the case of change, the supplier must inform the applicant. A supplier inspection programme must be available. The applicant can delegate analysis if he performs identification and periodically verifies the validity of the supplier's results. This information may be in the DMF for materials. Small volume parenterals (< 100 mL) and large volume parenterals (> 100 mL) are distinguished</p> <p>Certificate of analysis or certificate of certification</p>
Pharma. dev. (3.2.P2.4) or Stability (3.2.P8)	In the absence of migration studies performed during development. The study of leachables is performed during stability studies under normal and accelerated conditions	Stability : compatibility and safety studies can be performed during stability studies according to ICH conditions
Toxicological data (2)	For extractable and leachables, according to their quantity and chemical structure, even when they are approved in foodstuff regulations except when they are described in a Pharmacopoeia	« Safety » : toxicological evaluation (tests or literature) following studies of leachables

(1) The safety part comprises studies of leachables prior to their toxicological evaluation. (2) Data of the literature and test results should be provided in Module 2 section 2.6.6.8, Module 4 section 2.3.7.6.

laquelle des recommandations sont proposées par des organisations professionnelles de fabricants, de représentants de santé des autorités et d'utilisateurs. Ces organisations ont vu le jour ces dernières années pour fournir des guides ou un support technique à la validation des interactions contenant-contenu.

C'est le cas de l'association PQRI (Product Quality Research Institute), qui regroupe des membres du gouvernement (FDA), de l'industrie et des académies pour travailler sur les aspects de la qualité, la sécurité et la performance des produits pharmaceutiques. Un groupe de travail a élaboré un guide qui fait référence dans l'industrie pour l'évaluation des extractibles et des relargables, incluant les limites d'acceptation des relargables applicables aux dispositifs d'inhalation par voie orale ou intranasale [12].

Un second groupe de travail développe actuellement un texte équivalent pour les applications parentérales et ophtalmiques [13].

D'autre part, l'association BPSA (Bio-Process Systems Alliance), créée en 2005, regroupe en majorité des fournisseurs qui élaborent et partagent des guides pour faciliter l'adoption des systèmes à usage unique pour la production biopharmaceutique et de vaccins. Des recommandations ont été élaborées spécifiquement sur le sujet des extractibles [14]. Un guide spécifique a été édité en 2010.

LELSIE (Extractables and Leachables Safety Information Exchange) rassemble des adhérents issus de l'industrie pharmaceutique pour créer des bases de données d'extractibles et de relargables en mutualisant des études sur les principaux composés utilisés. La structure est partagée en deux groupes dont l'un prend en charge l'analyse des matériaux (information sur les relargables potentiels) et l'autre développe une base de données toxicologique.

IV MÉTHODOLOGIE

1. ANALYSE DE RISQUE INITIALE

L'établissement d'une étude de compatibilité pertinente pour les produits injectables nécessite une analyse de risque préalable. Elle permet de décider les études de compatibilité à réaliser et doit reposer sur une approche scientifique des conditions de mise en œuvre du contenu et de son contenant.

Cette analyse de risque sera réalisée en fonction des facteurs de risque mais aussi des données initiales du fournisseur.

1.1. Facteurs de risque

L'analyse de risque doit tenir compte de différents facteurs, dont :

- la voie d'administration parentérale,
- la posologie,
- le type et la nature du dispositif d'injection,
- les conditions d'utilisation du matériau,
- la composition du matériau et son processus de fabrication,

professional organizations, representatives of health authorities and users. Over recent years, these organizations have published guidelines or technical documents concerning validation of container-content interactions.

The Product Quality Research Institute (PQRI), composed of government (FDA), industry and academic representatives was formed to work on quality, safety and performance aspects of pharmaceutical products. A task force established references guidelines for industry for the evaluation of extractables and leachables including acceptable limits of leachables applicable to oral or intranasal inhalation devices [12].

A second working group is currently developing equivalent guidelines for parenteral and ophthalmic drug products [13].

The BPSA (Bio-Process Systems Alliance) association, created in 2005, is predominantly composed of suppliers, who elaborate and share guidelines to facilitate the adoption of disposable systems for biopharmaceutical production and vaccines. Specific guidelines concerning extractables have been elaborated [14]. A specific guide was published in 2010.

LELSIE (Extractables and Leachables Safety Information Exchange) is composed of members derived from the pharmaceutical industry to create extractables and leachables databases by sharing studies on the main compounds used. This organisation is divided into two groups, one in charge of analysis of materials (information on potential leachables) and the other that is developing a toxicological database.

IV METHODOLOGY

1. INITIAL RISK ANALYSIS

Risk analysis is a prerequisite to compatibility studies on parenteral preparations in order to determine what types of compatibility studies should be performed and must be based on a scientific approach to evaluate the potential interactions between container and content.

Risk analysis must be performed as a function of the risk factors but also the supplier's initial data.

1.1. Risk factors

Risk analysis must take various factors into account, including:

- parenteral route of administration,
- dosage,
- type and nature of the injection device,
- conditions of use of the material,
- composition of the material and its manufacturing process,

- les caractéristiques du médicament et son processus de fabrication (type et nature du matériel de fabrication en contact),
- le degré d'innovation du matériel (nouveau matériel ou changement d'une matière première par exemple).

1.1.1. Voies d'administration

Comme cela a été développé auparavant, la voie d'administration parentérale est une voie dite à résorption immédiate ou directe, c'est-à-dire dans laquelle 100 % de la dose administrée passe dans le milieu intérieur et se retrouvera immédiatement ou à terme dans le sang ou les tissus. Cette absence de barrière expose à un risque accru tant au regard de l'action du/des principe(s) actif(s) que des éventuels contaminants, dont l'ensemble des substances relargables du contenant. L'analyse de risque doit tenir compte de la voie parentérale utilisée et différencier des éventuels effets locaux ou généraux selon que la forme est destinée à une action topique ou systémique. Toutefois, il faut noter que même administré par voie sous-cutanée pour une action locale, un allergène contenu dans un injectable peut induire une réaction de sensibilisation systémique. En revanche, l'existence d'un fort effet de premier passage hépatique peut représenter un facteur de réduction du risque, en particulier dans la mesure où la voie de métabolisation de la molécule est connue.

1.1.2. Posologie

Les quantités administrées et les durées de traitement doivent être prises en compte dans l'analyse de risque. Un produit injecté une seule fois, type vaccin, ne présente pas les mêmes risques qu'un produit administré de façon chronique, type produit pour nutrition parentérale.

1.1.3. Type et nature du dispositif d'injection

Les dispositifs impliqués dans l'administration par voie parentérale peuvent être de différentes natures selon la posologie envisagée. On peut distinguer globalement deux grandes familles de dispositifs, ceux de faible volume (< 100 mL) destinés à une administration unique ou répétée sous forme espacée (seringues préremplies, flacons pour reconstitution des injectables, etc.) et ceux de grand volume (> 100 mL) (poches de perfusion ou de nutrition parentérale) impliquant généralement une administration prolongée et une quantité administrée élevée. Les rapports surface/volume et les quantités administrées étant totalement différents, ces dispositifs ne peuvent pas être soumis aux mêmes contraintes.

1.1.4. Conditions d'utilisation du matériau

La nature du contact du produit avec un matériau de conditionnement ou de fabrication doit être prise en compte. En effet, la fraction des extractibles totaux disponibles pour une migration est influencée par les

- characteristics of the medicinal product and its manufacturing process (type and nature of the manufacturing equipment in contact with the product),
- degree of innovation of the equipment (new equipment or change of starting material for example).

1.1.1. Routes of administration

As indicated above, the parenteral route of administration is a route allowing direct or immediate absorption, i.e. 100 % of the administered dose enters the internal environment and is immediately or subsequently detected in the blood or tissues. This absence of barrier is associated with an increased risk in relation to the action of active ingredient(s) and possible contaminants, including all leachable substances of the container. Risk analysis must take into account the parenteral route used and must distinguish the possible local and systemic effects according to whether the dosage form is intended to exert a topical or systemic action. However, it should be noted that even when administered by subcutaneous injection to exert a local action, an allergen contained in a parenteral can induce a systemic sensitization reaction. In contrast, an intense hepatic first-pass effect can represent a risk reduction factor, especially when the route of metabolism of the molecule is known.

1.1.2. Dosage

The quantities administered and the duration of treatment must be taken into account in the risk analysis. A product injected only once, as vaccines, does not present the same risk as a chronically administered product such as a parenteral nutrition product.

1.1.3. Type and nature of the injection device

Various types of devices can be used for parenteral administration according to the dosage considered. Globally, two main families of injection devices can be distinguished: low volume parenterals (< 100 mL) intended for single or repeated administration at distinct intervals (prefilled syringes, vials for reconstitution of parenteral preparations, etc.) and large volume parenterals (> 100 mL) (infusion or parenteral nutrition bags) generally requiring prolonged administration of large quantities. As the surface area/volume ratios and the quantities administered are completely different, these devices cannot be submitted to the same requirements.

1.1.4. Conditions of use of the material

The nature of the contact of the product with a packaging material or manufacturing equipment must be taken into account, as the fraction of total extractables available for migration is influenced by

facteurs suivants :

- durée : un contact temporaire (< 24 h) réduit la quantité d'extractibles disponibles lorsque l'extraction est limitée par une diffusion depuis l'intérieur de la masse du matériau par rapport au stockage prolongé (exemple : tubulure), mais ne limite pas le risque en cas d'extraction rapide, comme par exemple à travers une membrane de filtration ;
- rapport surface/volume : plus la surface en contact est grande par rapport au volume total du contenu, plus le risque est élevé ;
- température de fabrication ou stockage : pour une température comprise entre 0 °C et + 8 °C, l'impact est relativement faible. Celui-ci augmente avec la température ;
- proximité au produit final : au cours du processus de fabrication, différentes étapes de purification et de dilution permettent de réduire le risque de présence de substances issues du matériau dans le produit final ;
- contact direct ou indirect des éléments du packaging avec le contenu. Dans certains cas, certaines substances des éléments qui ne sont pas en contact direct avec la solution peuvent diffuser.

1.1.5. Composition du matériau et son processus de fabrication

La prédisposition à l'extraction d'un matériau dépend de la solubilité de l'extractible et de sa diffusion, en lien direct avec la structure, le poids moléculaire. Les matières plastiques et les élastomères sont les matériaux les plus problématiques en raison de leur composition complexe et de leur tendance à réagir avec de nombreux systèmes de solvants. Le processus de fabrication du matériau doit aussi être considéré, en particulier le processus de stérilisation. En tout état de cause, les essais devront être réalisés sur un matériel ayant suivi le même procédé de stérilisation que celui destiné à la production.

1.1.6. Caractéristiques du médicament et son processus de fabrication

Les caractéristiques physicochimiques du médicament doivent aussi être considérées.

Les formulations liquides présentent un risque d'extraction plus élevé par rapport à un produit lyophilisé et ces formulations représentent une part importante des formes à usage parentéral.

Certaines formulations en fonction du type de solvant (polarité) et de sa concentration influencent la migration et interviennent dans la définition du niveau de risque.

Le contenu de la forme à usage parentéral n'est en effet pas toujours composé d'une phase aqueuse tamponnée contenant un/des principe(s) actif(s) issus de la chimie pharmaceutique classique. D'une part la phase liquide peut être de nature faiblement polaire en raison de l'addition de co-solvants, voire apolaire (lipidique). Le caractère hydrophobe de ces phases est susceptible d'induire le relargage de composés apolaires du contenant qui, en présence d'un contenu

the following factors:

- duration: temporary contact (< 24 h) reduces the quantity of available extractables when extraction is limited by diffusion from the interior of the mass of the material compared to prolonged storage (e.g. tubing), but does not limit the risk in the case of rapid extraction, for example across a filtration membrane;
- surface area/volume ratio: the larger the surface area in contact compared to the total volume of the content, the higher the risk;
- manufacturing or storage temperature: for temperatures between 0 °C and + 8 °C, the impact is relatively low, but this impact increases as the temperature increases;
- proximity to the finished product: various purification and dilution steps during the manufacturing process reduce the risk of the presence of material compounds in the finished product;
- direct or indirect contact of packaging materials with the content. In some cases, certain compounds of packaging materials that are not in direct contact with the solution can diffuse into the solution.

1.1.5. Composition of the material and its manufacturing process

The susceptibility to extraction of a material depends on the solubility and diffusion of the extractable, which are directly related to the structure and molecular weight. Plastics and elastomers are the most problematical materials because of their complex composition and their tendency to react with a large number of solvent systems. The material manufacturing process must also be taken into account, particularly the sterilization process. In any case, tests must be performed on a material submitted to the same sterilization process as that intended for the manufacturing process.

1.1.6. Characteristics of the medicinal product and its manufacturing process

The physicochemical characteristics of the medicinal product must also be considered.

Liquid formulations present a higher risk of extraction than freeze-dried powders and represent a large share of parenteral preparations.

Some formulations, depending on the type of solvent (polarity) and its concentration, influence migration and have an impact on definition of the risk level.

The content of the parenteral preparation is not always composed of an aqueous buffer phase containing active ingredient(s) derived from classical pharmaceutical chemistry, as the liquid phase may be weakly polar due to the addition of co-solvents, or even nonpolar (lipid). The hydrophobic nature of these phases is likely to induce the release of non-polar compounds from the container, which would not have migrated in the presence of a hydrophilic

hydrophile, n'auraient pas migré. Des essais réalisés en utilisant une phase de polarité identique devront donc être réalisés lors des études d'extractible et de simulation.

D'autre part, si on dispose d'un recul important sur l'ensemble des principes actifs classiques, ceux issus des biotechnologies (peptides, protéines, acides nucléiques...) doivent conduire à des études détaillées spécifiques. L'interaction des protéines et peptides avec les surfaces est un phénomène dont l'importance varie considérablement selon la nature du couple considéré. Les protéines et peptides peuvent être de nature hydrophile ou hydrophobe et leur point isoélectrique couvre la quasi-totalité de la gamme de pH. Ainsi, dans un même tampon, une protéine ou un peptide pourra présenter une charge globale ou locale très variable favorisant ou non son interaction avec le contenant. Cette adhésion peut induire une dénaturation partielle ou totale et, bien que le phénomène soit normalement réversible, la protéine désorbée peut voir son potentiel immunogène fortement modifié.

De par sa large diffusion, l'insuline fait partie des peptides au regard desquels les études les plus nombreuses ont été réalisées. Selon les conditions de milieu et les polymères en contact, le pourcentage de fixation de l'insuline au support pourrait varier de 5 à 80 % [15, 16]. La fixation du peptide est dépendante de la température [17, 18], des charges et de la force ionique [19-21] dont l'intensité est telle qu'elle serait en mesure d'influer sur l'effet des traitements en unités de soins intensifs [22].

L'adsorption d'autres hormones peptidiques a fait l'objet d'études plus limitées. Ainsi il apparaît que l'adsorption de l'érythropoïétine et de l'hormone de croissance (GH) dans les poches et tubulures de perfusion serait inférieure à 7 % [23]. Inversement, l'adsorption du peptide natriurétique ANP sur un contenant en polystyrène peut dépasser les 70 % et affecter l'effet de la molécule [24]. Toutefois, dans la plupart des cas ce paramètre reste très mal, voire non maîtrisé.

La stérilisation du produit en fin de procédé de fabrication peut aussi générer des extractibles, les filtres utilisés pour la stérilisation en ligne étant aussi susceptibles de libérer des molécules indésirables. Si une étape de stérilisation du produit est réalisée dans le contenant, ce processus peut aussi favoriser la migration des substances issues du matériau.

1.2. Compilation des informations fournisseurs et qualification initiale des matériaux

Afin de pouvoir évaluer le risque initial des matériaux, le fournisseur, après signature d'un contrat de confidentialité, doit fournir la liste qualitative et quantitative des matériaux. Des informations sur le processus de fabrication sont également nécessaires. Les résultats des tests de biocompatibilité (USP <87>, USP <88> et USP <1031> ou ISO 10993), la conformité aux pharmacopées et aussi les profils d'extractibles sont également à prendre en compte pour l'analyse de risque.

content. Tests must therefore be performed on a phase with identical polarity during extractables and simulation studies.

On the other hand, although considerable experience has been acquired with conventional drug substances, specific detailed studies must be conducted on those derived from biotechnologies (peptides, proteins, nucleic acids, etc.). The degree of interaction of proteins and peptides with surfaces varies considerably according to the nature of the couples considered. Proteins and peptides can be hydrophobic or hydrophilic and their isoelectric point can be situated over almost the entire range of pH. Consequently, in the same buffer solution, a protein or peptide may present a highly variable global or local charge, which may or may not predispose to interaction with the container. Adhesion of proteins and peptides can induce partial or total denaturation and, although the phenomenon is normally reversible, the immunogenic potential of the desorbed protein can be markedly modified.

Due to its widespread use, insulin is one of the most extensively studied peptides. Depending on the conditions of the suspension and the polymers in contact, the percentage binding of insulin to the container surface may vary from 5 to 80 % [15, 16]. Peptide binding is dependent on temperature [17, 18], charge and ionic strength [19-21], the intensity of which can influence the effect of treatment in intensive care units [22].

Adsorption of other peptide hormones has been studied less extensively. For example, the adsorption of erythropoietin and growth hormone (GH) in infusion bags and tubing appears to be less than 7 % [23]. Conversely, adsorption of atrial natriuretic peptide (ANP) onto a polystyrene container can exceed 70 % and can alter the effect of the molecule [24]. However, in most cases, this parameter remains uncontrolled or only very poorly controlled.

Sterilization of the product at the end of the manufacturing process can also generate extractables, as the filters used for on-line sterilization can release undesirable molecules. When a product sterilization step is performed in the container, this process can also promote migration of packaging material compounds.

1.2. Compilation of supplier information and initial material qualification

In order to evaluate the initial risk of materials, and after signing a confidential agreement, the supplier must provide the qualitative and quantitative list of materials. Information on the manufacturing process is also necessary. The results of biocompatibility tests (USP <87>, USP <88> and USP <1031> or ISO 10993), compliance with Pharmacopoeias and extractables profiles must also be taken into account for risk analysis.

Tableau 5. Qualification initiale type des matériaux.
Table 5. Standard initial qualification of materials.

Matériaux/composants / Materials/components	Qualification initiale/Initial qualification
Résine/Resin	Tests Pharmacopée (Ph. Eur et/ou USP) ou monographie interne Pharmacopoeia tests (Ph. Eur and/or USP) or in-house monograph
Pièces injectées (bouchons, port système...) Molded parts (stoppers, port system, etc.)	Tests Pharmacopée (Ph. Eur. et/ou USP) ou monographie interne/Pharmacopoeia tests (Ph. Eur and/or USP) or in-house monograph Biocompatibilité (USP, ISO)/Biocompatibility (USP, ISO) Profil d'extractible/Extractables profile
Emballage vide (poche, flacon seringue) Empty packaging (bag, vial, syringe)	Tests Pharmacopée (Ph. Eur. et/ou USP) ou monographie interne/Pharmacopoeia tests (Ph. Eur and/or USP) or in-house monograph Biocompatibilité (USP, ISO)/Biocompatibility (USP, ISO) Profil d'extractible/Extractables profile

Tableau 6. Biocompatibilité et propriétés physicochimiques.
Table 6. Biocompatibility and physicochemical properties.

Description équipement de fabrication Description of manufacturing equipment	Qualification fournisseur Supplier qualification
Containers	Tests pharmacopées (Ph.Eur, USP, CFR...)/Pharmacopoeia tests (Ph. Eur, USP, CFR, etc.) Biocompatibilité (USP, ISO...)/Biocompatibility (USP, ISO, etc.) Guide d'extractibles/Extractables guide Compatibilité/résistance chimique/Compatibility/chemical resistance Validation de la stérilisation (lorsque dispositif stérile)/Validation of sterilization (in the case of sterile devices) Validation de l'intégrité/Validation of integrity
Filtres/Filters	Tests pharmacopées (Ph.Eur, USP, CFR...)/Pharmacopoeia tests (Ph. Eur, USP, CFR, etc.) Biocompatibilité (USP, ISO...)/Biocompatibility (USP, ISO, etc.) Guide d'extractibles/Extractables guide Compatibilité/résistance chimique/Compatibility/chemical resistance Validation de la stérilisation (lorsque dispositif stérile)/Validation of sterilization (in the case of sterile devices) Validation de l'intégrité/efficacité de la filtration/Validation of filtration integrity/efficacy
Tubes, connexions/Tubes, connections	Tests pharmacopées (Ph.Eur, USP, CFR...)/Pharmacopoeia tests (Ph. Eur, USP, CFR, etc.) Biocompatibilité (USP, ISO...)/Biocompatibility (USP, ISO, etc.) Compatibilité/résistance chimique/Compatibility/chemical resistance Propriétés physiques/Physical properties

D'autres critères réglementaires doivent être considérés : conformité BSE/TSE (*bovine spongiform encephalopathy/transmissible spongiform encephalopathy*) pour les additifs tels que les stéarates issus des graisses animales ; le fabricant doit suivre la réglementation européenne REACH, qui implique l'absence de certaines substances chimiques [25] ; le matériel est soumis à une qualification initiale (tableau 5).

Au cours du processus de fabrication des substances actives ou du produit fini injectable, le produit injectable sera en contact avec des dispositifs à usage unique en matières plastiques (tubes, filtres containers, connecteurs...), en verre ou des équipements en acier inoxydable. La qualité des équipements de production doit être ainsi évaluée et la qualité des matériaux sécurisée. La biocompatibilité et les propriétés physicochimiques répertoriées dans le tableau 6 participeront à la fiabilisation du processus de production des produits injectables.

Les tests sont réalisés par le fournisseur ou par le fabricant de médicaments.

Un contrat qualité couvrant la « notification des changements et modifications » avec les fournisseurs préalablement qualifiés doit également être établi dès le début du développement du packaging. Ce contrat permet de garantir que la composition des différents matériaux reste inchangée. Si un changement est inévitable, le fournisseur doit prévenir le client du changement dans des délais négociés. De plus, si une

Other regulatory criteria must be considered: BSE/TSE compliance (*bovine spongiform encephalopathy/transmissible spongiform encephalopathy*) for additives such as stearates derived from animal tallow; the manufacturer must comply with European REACH regulation, requiring the absence of certain chemical compounds [25]; the material must be submitted to initial qualification (Table 5).

During the manufacturing process of active substances or the finished product, the parenteral preparation is in contact with plastic disposable devices (tubing, filters, containers, connectors, etc.), glass or stainless steel equipment. The quality of manufacturing equipment must therefore be evaluated and the quality of materials must be ensured. The biocompatibility and physicochemical properties listed in Table 6 participate in quality assurance of the parenteral preparation manufacturing process.

These tests are performed by the supplier or by the medicinal product manufacturer.

A quality contract covering “notification of changes and modifications” with previously qualified suppliers must also be established right from the start of packaging development. This contract is designed to ensure that the composition of the various materials remains unchanged. If a change is unavoidable, the supplier must inform the customer about the change within a defined timeframe. Furthermore, when the

Tableau 7. Évaluation du risque d'interaction matériaux en contact avec le médicament en cours de fabrication (d'après [26]).
Table 7. Evaluation of the risk of interactions with materials in contact with the medicinal product during manufacture (from [26]).

Risk variable	Risk level	Risk value	Product risk index
Material type	Reactive	10	1
	Interactive	5	
	Inert	1	
Extraction strength of solution	Organic	10	1
	Water/organic	5	
	Water	1	
Contact duration	> 30 days	10	5
	24 h to 30 days	5	
	< 24 h	1	
Contact surface area	> 5000 cm ²	10	5
	2000-5000 cm ²	5	
	< 2000 cm ²	1	
Contact temperature	> 70 °C	10	5
	25-70 °C	5	
	< 25 °C	1	
Proximity to finished product	Final product	10	10
	Purified to final product	5	
	Remote from final product	1	
Total risk index (< 20: low, 20-50: moderate, 50-60: high, > 60: reject)			27

modification de la formulation doit avoir lieu, cela permet d'augmenter les stocks et d'anticiper le changement afin d'éviter toute rupture de disponibilité. Un audit régulier du fournisseur devrait être planifié.

1.3. Niveaux de risque

L'évaluation du risque peut être réalisée en faisant appel à des méthodes classiques comme l'AMDEC, avec une cotation des différents paramètres critiques et l'aboutissement à des niveaux de risque (faible/moyen/élevé ou significatif/non significatif).

En fonction des résultats de l'analyse de risque, la documentation et les qualifications fournies par le fournisseur des équipements peuvent s'avérer suffisantes pour justifier un processus de fabrication maîtrisé. Dans d'autres cas, il sera recommandé de mener des études d'interaction complémentaires (exemple : compatibilité chimique, relargable ou performance). Un exemple est donné dans le *tableau 7*.

2. PROFIL D'EXTRACTIBLES, SIMULATION ET RELARGABLES

Une fois l'analyse de risque faite par l'utilisateur et la qualification initiale faite par le fournisseur, le matériel peut être soumis si nécessaire à une qualification par l'utilisateur qui pourra comprendre trois étapes :

- profil d'extractibles (si insuffisamment documenté),
- simulation,
- étude de relargables.

Si un matériel préalablement qualifié subit un changement de formulation, une analyse de risque devra déterminer quel type d'analyse est nécessaire pour approuver ce changement. Un profil d'extractibles comparatif est souvent suffisant.

formulation needs to be modified, this advance notification allows stocks to be increased in anticipation of the change to avoid product shortages. Regular supplier audit must be conducted.

1.3. Risk levels

Risk assessment can be based on conventional methods such as FMECA, with scoring of the various critical parameters, resulting in risk levels (low/medium/high or significant/not significant).

Depending on the results of risk assessment, the documentation and qualifications provided by the equipment supplier may be sufficient to justify a controlled manufacturing process. Additional interaction studies e.g.: chemical compatibility, leachables or performance, may be recommended in other cases. An example is given in *Table 7*.

2. EXTRACTABLES PROFILE, SIMULATION AND LEACHABLES

After completion of risk analysis by the user and initial qualification by the supplier, the material can be submitted, when necessary, to qualification by the user, which may comprise three steps:

- extractables profile (if insufficiently documented),
- simulation,
- leachables study.

In the event of a change of formulation of a previously qualified material, risk analysis must determine what type of analysis is required to approve this change. A comparative extractables profile is often sufficient.

2.1. Profil d'extractibles et simulation

2.1.1. Extractibles

Le profil d'extractibles doit être établi lors de la qualification initiale du matériel ou si nécessaire lors d'un changement de formulation du matériel. Il permet d'identifier les produits extractibles potentiels et d'en obtenir la liste exhaustive.

Il convient de choisir des solvants de polarités différentes et d'avoir au moins un solvant représentatif de la matrice finale. Cette étude est réalisée dans des conditions extrêmes sans entraîner de dégradation du matériau (reflux, haute température).

La liste des extractibles obtenue lors de cette étude permet de cibler les composés potentiels qui pourraient être relargués pour une formulation donnée. Ce profil peut aussi être utilisé pour le suivi qualité des emballages.

Des exemples de protocoles contenant des conditions d'extraction à appliquer sont donnés dans les normes ou la littérature (norme ISO, PQRI, pharmacopées, BPSA).

2.1.2. Simulation

L'étude de simulation a pour but d'identifier les relargables probables. Elle est réalisée dans des conditions et des milieux de simulation représentatifs de l'utilisation finale du matériau, idéalement un placebo. Ces conditions sont plus stressantes que les conditions normales d'utilisation mais moins sévères que les conditions appliquées pour les études d'extractibles [27].

La simulation peut aussi être réalisée pour les composants qui ne sont pas en contact direct avec la solution.

On distinguera les profils d'extraction et de simulation standard de ceux pour des matériaux qui ne sont pas en contact direct avec la solution mais susceptibles de migrer dans le contenu. Par exemple, pour l'étude d'une encre d'une poche injectable, le profil d'extractibles sera établi en surimprimant une poche puis en mettant en contact direct des morceaux de cette poche dans différents solvants à des conditions extrêmes de température (reflux...).

Un profil d'extractible sera établi en comparant avec une poche non imprimée. Les mêmes techniques analytiques seront ensuite utilisées pour l'étape de simulation. La simulation consiste à surimprimer une poche mais cette fois à la remplir et à lui faire subir des conditions de températures accélérées sur un plus long terme. Lors de cette étape, l'encre n'est pas en contact direct avec la solution et les conditions sont ainsi plus réalistes tout en restant sévères.

À la suite de ses études d'extractible et de simulation, une évaluation toxicologique sera réalisée et permettra d'identifier les substances à suivre lors des études de relargables.

2.1. Extractables profile and simulation

2.1.1. Extractables

The extractables profile must be established at the time of initial qualification of the material or, when necessary, after a change of formulation of the material. This profile identifies and establishes a comprehensive list of potential extractable products.

Solvents with different polarities should be used, including at least one solvent representative of the final matrix. This study must be conducted under aggressive conditions, but without inducing degradation of the material (reflux, high temperature).

The list of extractables obtained during this study is used to target potential compounds that could be released from a given formulation. The extractables profile can also be used for packaging quality monitoring.

Examples of protocols indicating the extraction conditions to be applied are presented in standards and in the literature (ISO standards, PQRI, Pharmacopoeias, BPSA).

2.1.2. Simulation

The simulation study is designed to identify probable leachables. It is performed under conditions and using simulation media representative of the final use of the material, ideally a placebo. These conditions are more stressful than normal use conditions, but less severe than the conditions applied to extractables studies [27].

Simulation can also be performed on components that are not in direct contact with the solution.

Standard extraction and simulation profiles must be distinguished from those concerning materials not in direct contact with the solution but able to migrate into the content. For example, when studying the ink of a bag of solution for infusion, the extractables profile must be established by over-printing a bag and by placing pieces of this bag in direct contact with the various solvents at aggressive temperature conditions (reflux, etc.).

An extractables profile must be established in comparison with a non-printed infusion bag. The same analytical techniques are then used for the simulation step. Simulation consists of over-printing a bag, which is then filled and submitted to accelerated temperatures conditions for a longer period of time. During this step, the ink is not in direct contact with the solution and the test conditions are therefore more realistic, while still remaining severe.

After completing extractables studies and simulation, a toxicological assessment is performed to identify the compounds that must be monitored during leachables studies.

2.2. Étude des relargables

L'étude de relargables est faite en présence d'un placebo de propriétés physicochimiques identiques à celles de la formulation médicamenteuse, voire avec la solution finale si cela est possible.

Elle est réalisée dans des conditions normales de conservation du produit, *a minima* à T₀, demi-vie et fin de vie du produit.

La concentration des substances sélectionnés sera suivie aux différents termes de stockage. Les méthodes analytiques incluant la préparation d'échantillon seront développées et validées dans la matrice finale.

3. ÉVALUATION TOXICOLOGIQUE

3.1. Approche pragmatique

La démarche de l'évaluation toxicologique peut être abordée suivant une approche littérale de la réglementation, dont l'expérience montre qu'elle ne répond pas à tous les cas, ou suivant une approche pragmatique qui nécessite d'intégrer plusieurs facteurs d'adaptation. Ainsi, l'application stricte de la directive européenne [10] impose pour les formes à usage parentéral (ou oculaire), et sauf argument contraire, l'évaluation toxicologique de tout relargable potentiel selon sa structure et sa quantité. Le coût et les délais induits par une telle approche n'étant pas réalistes, ni justifiables dans tous les cas, l'expérience montre qu'avant de recourir à des tests toxicologiques expérimentaux, il est possible d'exclure des tests tout ou partie des relargables détectés grâce à une analyse de risque et au calcul de valeurs limites acceptables sur le plan toxicologique.

3.2. Limites acceptables

3.2.1. Seuils toxicologiques

Les produits pour inhalation ont été les premiers à bénéficier de recommandations concernant les extractibles et relargables. Le Product Quality Research Institute (PQRI), structure collaborative associant la FDA, des industriels et des membres des académies, a en effet défini un seuil de sécurité (ou *safety concern threshold*, SCT) pour ces produits. Le SCT procède de la même approche probabilistique que le *threshold of toxicological concern* (TTC) appliqué pour les impuretés génotoxiques dans le principe actif ou le produit fini [28]. Cependant, la valeur retenue pour le SCT sera différente selon le niveau de risque choisi.

En dessous de la valeur du SCT un extractible (ou relargable) est considéré comme présentant un risque (carcinogène ou non carcinogène) « acceptable » pour la santé humaine. La valeur de SCT a été fixée sur la base de la Carcinogen Potency DataBase en référence au risque génotoxique ou cancérigène, et pour un individu de 50 à 70 kg. Pour une probabilité de survenue de cancer de 1 sur 10⁶, le SCT est de 0,15 µg/j, valeur retenue par le PQRI pour les pro-

2.2. Leachables study

The leachables study is performed in the presence of a placebo with identical physicochemical properties to those of the drug formulation, or even with the final solution whenever possible.

This study is performed under normal storage conditions of the product, at least at T₀, half-life and at the end of the product shelf-life.

The concentrations of the target compounds are followed at various storage times. Analytical methods including sample preparation are developed and validated in the final matrix.

3. TOXICOLOGICAL ASSESSMENT

3.1. Pragmatic approach

The toxicological assessment can be conducted according to an approach based on literal interpretation of the regulations, although experience shows that it is not strictly applicable to all cases, or according to a pragmatic approach which requires integration of several adjustment factors. Strict application of the European Directive [10] for medicinal products for parenteral (or ocular) administration, except when otherwise specified, requires toxicological assessment of all potential leachables according to their molecular structure and quantity. As the costs and time required by this type of approach are unrealistic and not always justified, experience has shown that, before conducting experimental toxicity tests, tests for all or part of the leachables detected can be excluded by means of risk analysis and calculation of toxicologically acceptable thresholds.

3.2. Acceptable limits

3.2.1. Toxicological thresholds

Guidelines concerning extractables and leachables were first defined for preparations for inhalation. The Product Quality Research Institute (PQRI), a collaborative structure associating the FDA, manufacturers and academics, has defined a safety concern threshold (SCT) for these products. The SCT is determined according to the same probabilistic approach as the threshold of toxicological concern (TTC) applied to genotoxic impurities in the active ingredient or finished product [28]. However, the value of SCT varies according to the risk level adopted.

Below the SCT value, an extractable (or leachable) is considered to present an "acceptable" risk (carcinogenic or noncarcinogenic) for human health. The SCT is defined on the basis of the Carcinogen Potency DataBase with reference to the genotoxic or carcinogenic risk for an individual weighing 50 to 70 kg. For a probability of developing cancer of 1 out of 10⁶, the SCT is 0.15 µg/day, the value adopted by the PQRI for preparations for inhalation. For

duits pour inhalation. Pour les produits injectables et produits ophtalmiques, c'est une probabilité de cancer de 1 sur 10^5 qui, selon le PQRI, resterait acceptable et fixerait le SCT à 1,5 µg/j [27].

Aucun produit potentiellement carcinogène ne doit être présent au-delà du SCT ; cependant, un complément d'information sur sa non-carcinogénicité (évaluation *in silico* ou références bibliographiques) peuvent permettre de le dédouaner.

L'approche du SCT (ou TTC déjà employée pour les impuretés génotoxiques) n'est pas mentionnée dans la *guideline* européenne [10].

Une autre notion de seuil a été décrite par le PQRI : le seuil de qualification (ou *qualification threshold*, QT). Les substances non carcinogènes sont jugées comme qualifiées d'un point de vue toxicologique jusqu'à cette valeur limite fixée par le PQRI à 5 µg/j pour les produits d'inhalation (en discussion pour les injectables). Au-delà du QT, le risque n'est plus acceptable et une évaluation toxicologique doit être réalisée sur les substances. De plus, il est impératif d'identifier les substances présentes à une concentration supérieure au QT.

3.2.2. Transposition en limites analytiques

À partir de la notion de SCT a été conçu l'*analytical evaluation threshold* (AET), développé par le PQRI en premier lieu pour les produits pour inhalation et les voies nasales [30]. L'AET permet d'établir un seuil analytique à partir duquel les substances devront être considérées et quantifiées. Leur identification peut être approximative. Les substances présentes à une concentration inférieure à l'AET sont compatibles avec un risque acceptable, qu'elles soient carcinogènes ou non carcinogènes, donc indépendamment de toute étude toxicologique (*cf.* [29], p. 181-184).

L'AET se calcule pour un échantillon donné, qu'il provienne du produit fini lors de l'étude des relargables ou d'un matériau lors de l'étude des extractibles.

Le passage d'une valeur de SCT à un AET final s'effectue après avoir estimé l'AET en prenant en compte différents paramètres tels que : la « dose » (en volume ou en masse de produit fini) administrée par jour, et/ou, selon l'expression de l'AET estimé, le nombre d'articles de conditionnement utilisés pour une « dose » journalière ou la masse du matériau considéré dans l'article de conditionnement.

1) AET estimé en µg/mL de produit fini :

$$\text{AET estimé (}\mu\text{g/mL ou ppm)} = \frac{\text{SCT (}\mu\text{g/j)}}{\text{« dose » journalière (vol. injecté) (mL/j)}}$$

avec SCT = 1,5 µg/j (recommandation PQRI pour les injectables et produits ophtalmiques).

2) AET estimé en µg/article de conditionnement :

$$\text{AET estimé (}\mu\text{g/article)} = \frac{\text{SCT (}\mu\text{g/j)}}{N}$$

avec SCT = 1,5 µg/j (recommandation PQRI pour les injectables et produits ophtalmiques) et N = nombre d'articles de conditionnement pour une « dose » journalière.

parenteral and ophthalmic preparations, a cancer probability of 1 out of 10^5 , corresponding to an SCT of 1.5 µg/day, would remain acceptable according to the PQRI [27].

No potentially carcinogenic product must be present at levels higher than the SCT. However, additional information on the absence of carcinogenicity of the substance (*in silico* evaluation or literature references) can allow clearance of such products.

The SCT approach (or TTC already used for genotoxic impurities) is not indicated in the European guideline [10].

Another threshold concept has been described by the PQRI: the qualification threshold (QT). Non-carcinogenic substances are considered to be toxicologically qualified up to this threshold defined by the PQRI of 5 µg/day for preparations for inhalation (under discussion for parenteral preparations). Beyond the QT, the risk is no longer acceptable and a toxicological assessment of the substances must be performed. It is also essential to identify substances present at concentrations higher than the QT.

3.2.2. Transposition into analytical thresholds

The AET (analytical evaluation threshold), based on the SCT concept, was developed by the PQRI primarily for preparations for inhalation and nasal routes [30]. The AET establishes an analytical threshold beyond which substances must be taken into account and quantified. Identification of such substances can be approximate. Substances present at concentrations less than the AET are compatible with an acceptable risk, whether or not they are carcinogenic and therefore independently of any toxicological analysis (*cf.* [29], p. 181-184).

The AET is calculated for a given sample derived from the finished product during the leachables study or a material during the extractables study.

An SCT value is transformed into a final AET value after estimating the AET by taking various parameters into account, such as: the daily dose (volume or mass of finished product) and/or, depending on the expression of the estimated AET, the number of primary packaging materials used for a daily dose or the mass of the material considered in the packaging material.

1) Estimated AET in µg/mL of finished product:

$$\text{Estimated AET (}\mu\text{g/mL or ppm)} = \frac{\text{SCT (}\mu\text{g/day)}}{\text{daily "dose" (vol. injected) (mL/day)}}$$

where SCT = 1.5 µg/day (PQRI recommendation for parenteral and ophthalmic preparations).

2) Estimated AET in µg/packaging material:

$$\text{Estimated AET (}\mu\text{g/article)} = \frac{\text{SCT (}\mu\text{g/day)}}{N}$$

where SCT = 1.5 µg/day (PQRI recommendation for parenteral and ophthalmic preparations), N = number of packaging materials for a daily dose.

3) AET estimé en µg/g de matériau :

$$\text{AET estimé (}\mu\text{g/g ou ppm)} = \frac{\text{SCT (}\mu\text{g/j)}}{\text{M} \times \text{N}}$$

avec SCT = 1,5 µg/j (recommandation PQRI pour les injectables et produits ophtalmiques), M = masse en g du matériau considéré dans l'article de conditionnement, N = nombre d'articles de conditionnement pour une « dose » journalière.

À l'AET estimé, le PQRI recommande d'ajouter un facteur de sécurité de 2. Cette valeur permet d'intégrer à la fois l'incertitude analytique et les facteurs de réponse des substances relarguées ou extraites. À un stade précoce de l'étude, un facteur de réponse moyen peut être calculé sur un ensemble de substances de référence et avec des méthodes non validées.

$$\text{AET final} = \frac{\text{AET estimé}}{\text{facteur de sécurité}}$$

avec facteur de sécurité recommandé par le PQRI = 2.

L'expression de l'AET en µg/article de conditionnement peut s'avérer pratique lorsque plusieurs tailles de contenant sont utilisées pour parvenir à une même dose journalière, comme illustré dans l'exemple ci-dessous.

Exemple d'application de l'AET

Calcul de l'AET

Soit un produit injectable administré de manière chronique avec une dose journalière de 10 mL. Le produit est disponible sous deux conditionnements, un flacon de 10 mL ou un flacon de 5 mL, tous les deux fermés par un bouchon identique en élastomère d'une masse de 2 g. Les différents seuils peuvent être exprimés comme présenté dans le *tableau 8*.

Utilisation de l'AET

Avant la mise en œuvre analytique, on tiendra compte des valeurs d'AET calculées selon le nombre d'articles de conditionnement maximum nécessaires pour parvenir à la dose journalière, cela afin d'identifier le pire des cas parmi les différentes possibilités d'administration. La valeur la plus stricte est celle retenue lors de l'analyse.

Interprétation des résultats

Les substances au-dessus de l'AET final seront identifiées (au moins approximativement), quantifiées puis comparées à une valeur limite toxicologique (SCT ou seuil toxicologique pertinent).

3) Estimated AET in µg/g of material:

$$\text{Estimated AET (}\mu\text{g/g or ppm)} = \frac{\text{SCT (}\mu\text{g/day)}}{\text{M} \times \text{N}}$$

where SCT = 1.5 µg/day (PQRI recommendation for parenteral and ophthalmic preparations, M = mass in g of the material considered in the packaging material, N = number of packaging materials for a daily dose.

The PQRI recommends adding a safety factor of 2 to the estimated AET. This safety factor is designed to integrate both the analytical uncertainty and response factors of the substances released or extracted. At an early stage of the study, a mean response factor can be calculated for all reference substances, using non-validated methods.

$$\text{Final AET} = \frac{\text{estimated AET}}{\text{safety factor}}$$

where safety factor recommended by the PQRI = 2.

Expression of the AET in µg/packaging material may be a more practical solution when several container sizes are used to deliver the same daily doses, as illustrated by the following example.

Example of application of the AET

Calculation of the AET

For a parenteral preparation administered chronically at a daily dose of 10 mL and available in two different packagings, a 10 mL vial or a 5 mL vial, both sealed by an identical elastomer stopper weighing 2 g, the various thresholds can be expressed as follows (*Table 8*).

Use of the AET

AET values calculated according to the maximum number of packaging materials necessary to obtain the daily dose must be taken into account before starting the analysis in order to identify the worst case among the various possibilities of administration. The strictest value is then used during the analysis.

Interpretation of the results

Substances with values above the final AET will be identified (at least approximately), quantified and then compared to a toxicological threshold (SCT or relevant toxicological threshold).

Tableau 8. Différentes expressions de l'AET. Exemple : « dose » = 10 mL, articles de conditionnement : flacons en verre de 5 ou 10 mL fermés par un bouchon en élastomère, matériau/élastomère (bouchon) : 2 g.

Table 8. Various expressions of AET. Example: dose = 10 mL, packaging materials: 5 or 10 mL glass vials sealed by an elastomer stopper, material/elastomer (stopper): 2 g.

SCT (µg/j) (µg/day)	AET estimé Estimated AET (ppm ou/or µg/mL)	AET final* Final AET (ppm ou/or µg/mL)	AET final* Final AET (1 x 10 mL) (µg/article)	AET final* Final AET (2 x 5 mL) (µg/article)	AET final* Final AET (1 x 10 mL) (µg/g elastomère/elastomer)	AET final* Final AET (2 x 5 mL) (µg/g elas- tomère/elastomer)
1.5	0.15	0.075	1.5	0.75	0.75	0.375

*Facteur de sécurité égal à 2/*Safety factor equal to 2.



- Étude d'extractibles : pour un résultat R exprimé en µg/g d'élastomère, la quantité de substance injectée par jour est :

$$R (\mu\text{g/g}) \times (N \times M)_{\text{dose journalière}}$$

avec N : nb de contenant/« dose » journalière, M : masse d'élastomère par contenant en g.

À comparer à une valeur de SCT ou PDE en µg/j.

- Étude de relargables : pour un résultat R exprimés en µg/mL de produit fini (dans le(s) conditionnement(s) considéré(s)), la quantité de substance injectée par jour est :

$$R (\mu\text{g/mL}) \times \text{« dose » journalière} \\ (\text{volume injecté en mL})$$

À comparer à une valeur de SCT ou PDE en µg/j.

3.2.3. Évolutions des limites

Sur la base de la relation structure/activité des molécules d'intérêt (selon le modèle QSAR), le PQRI rédige actuellement des recommandations pour les produits parentéraux et ophtalmiques en se reposant sur ce principe [27].

Dans leurs premières communications [31], les molécules pouvaient être classées selon cinq classes différentes avec un seuil toxicologique affecté à chaque classe (tableau 9).

Les classes I à III représentent des groupes de molécules exempts d'un caractère génotoxique, irritant ou sensibilisant ; la classe I regroupe les substances dont les risques associés à la structure sont les plus faibles et la classe III, les risques les plus élevés. La classe IV regroupe les molécules ne présentant pas d'alerte de génotoxicité mais un potentiel irritant ou sensibilisant. Enfin la classe V est réservée aux substances génotoxiques ou potentiellement génotoxiques.

La catégorisation s'effectue principalement par des moyens *in silico* comme Derek pour l'évaluation du potentiel génotoxique ou les règles de Cramer [32] étendues, pour la classification I à III. Un outil gratuit (ToxTree) est d'ailleurs proposé par l'Union européenne pour faciliter la classification d'une molécule selon les règles de Cramer (I à III) [33, 34].

Pendant, les seuils affectés et le nombre de classes à distinguer qui sont toujours en discussion au sein du groupe de toxicologistes du PQRI [27] a conduit ces derniers à faire une nouvelle proposition. Les dernières communications semblent indiquer qu'une simplification est envisagée, en ne proposant que trois classes et trois seuils toxicologiques correspondants (tableau 10).

Les réflexions sont toujours en cours et plus particulièrement sur la classe III (ancienne classe V) afin de garder une cohérence avec les discussions d'har-

- Extractables study: for a result R expressed in µg/g of elastomer, the quantity of substance injected per day is:

$$R (\mu\text{g/g}) \times (N \times M)_{\text{daily dose}}$$

where N: number of containers/daily dose, M: mass of elastomer (g) per container.

To be compared with an SCT or PDE value in µg/day.

- Leachables study: for a result R expressed in µg/mL of finished product (in the packaging(s) considered), the quantity of substance injected per day is:

$$R (\mu\text{g/mL}) \times \text{daily dose} \\ (\text{volume injected in mL})$$

To be compared with an SCT or PDE value in µg/day.

3.2.3. Threshold values evolution

The PQRI is currently preparing guidelines for parenteral and ophthalmic preparations based on the principle of the structure/activity relationship of the molecules of interest (according to the QSAR model) [27].

In their first report [31], molecules could be classified according to 5 different classes with a toxicological threshold attributed to each class (Table 9).

Classes I to III represent groups of molecules devoid of any genotoxic, irritant or sensitizing effects; class I comprises substances with the lowest structure-related risks and class III comprises substances with the highest risk. Class IV comprises molecules not presenting a genotoxicity alert, but an irritant or sensitizing potential. Finally, class V corresponds to genotoxic or potentially genotoxic substances.

Classification is essentially based on *in silico* techniques, such as Derek for evaluation of the genotoxic potential or extended Cramer's rules [32] for classes I to III. A free tool (ToxTree) is also proposed by the European Union to facilitate classification of a molecule according to Cramer's rules (class I to III) [33, 34].

However, the thresholds attributed and the number of classes to be distinguished are still under discussion by the PQRI toxicologists [27] who have made a new proposal. The latest communications appear to indicate that a simplified classification is under consideration, which will comprise only 3 classes and 3 corresponding toxicological thresholds (Table 10).

Discussions are still underway, particularly concerning class III (former class V) in order to maintain consistency with harmonization discussions on the

Tableau 9. Classification initiale basée sur ToxTree et Derek [31].
Table 9. Initial classification based on ToxTree and Derek [31].

	I	II	III	IV		V
				irritant	sensibilisant sensitizing	
Niveau toxicologique (µg/j) Toxicological level (µg/day)	150	45	75	5	5	0.15



Tableau 10. Proposition de classification [27].
Table 10. Proposed classification [27].

Classes initialement proposées Classes initially proposed	I	II	III	IV		V
				irritant	sensibilisant sensitizing	
Nouvelle proposition New class proposal	I			II		III
Niveau toxicologique (µg/j) Toxicological level (µg/day)	150			5		1.5 ou plus à définir/or more to be defined

monisation de la réglementation sur les impuretés génotoxiques (ICH M7).

3.2.4. Cas des grands volumes

L'application des seuils (SCT ou QT) transposés en limites analytiques s'avère bien plus difficile dans le cas de produits administrés en grands volumes (solutés de perfusion par exemple) que dans le cas de petits volumes en injection unique (vaccins) car le calcul abaisse l'AET considérablement, conduisant à rechercher et évaluer un nombre très élevé de molécules d'extractibles dans les études. Avec une valeur de SCT fixée à 1,5 µg/j pour les injectables, à confirmer par le PQRI, l'AET apparaît plus réaliste, en particulier dans le cas des larges volumes parentéraux.

3.3. Utilisation des extractibles totaux

Une évaluation préliminaire de la toxicité des extractibles totaux peut être envisagée, notamment dans le cas où il y a un défaut d'information sur les composants des matériaux en contact avec les produits et où l'identification de chaque composé pouvant migrer ou interagir s'avère délicate. Dans ce cas, l'absence de toxicité des extractibles totaux, démontrée grâce à une série de tests *in vitro* et/ou *in vivo*, viendrait compléter l'analyse de risque dans un sens favorable à la maîtrise du risque toxicologique.

Les échantillons utilisés pour les tests toxicologiques sont obtenus de préférence avec la formulation finale. Mais si le principe actif présente une toxicité propre, l'utilisation d'un placebo (véhicule sans principe actif) pourrait être la seule solution acceptable.

Lors de l'évaluation préliminaire, des analyses complémentaires peuvent être réalisées sur les extractibles totaux, par exemple les résidus non volatiles (NVR), le carbone organique total (TOC), qui donnent des informations sur la quantité de substances extraites par dose administrée que l'on peut comparer ensuite à un seuil acceptable, applicable pour un extractible individuel inconnu génotoxique (valeur de la TTC en discussion).

D'autre part, le risque est évalué avec les informations du fournisseur telles que :

- la famille du plastique (polyesters, polycarbonate, etc.) : ce qui informe sur une liste potentielle d'extractibles,
- la déclaration de l'absence des composés d'alerte, identifiés comme indicateurs d'une éventuelle activité cancérogène-génotoxique.

regulations on genotoxic impurities (ICH M7).

3.2.4. Large volume parenterals

The application of thresholds (SCT or QT) transposed to analytical limits is much more difficult for large volume parenterals (e.g. infusion solutions) than for single injection of small volume parenterals (vaccines), as the calculation considerably lowers the AET, leading to testing and evaluation of a very large number of molecules in extractable studies. With a SCT set at 1.5 µg/day for parenterals, yet to be confirmed by PQRI, the AET appears to be more realistic, particularly in the case of large volume parenterals.

3.3. Use of total extractables

Preliminary evaluation of the toxicity of total extractables can be considered, especially when insufficient information is available concerning the composition of materials in contact with the medicinal product and when identification of each compound likely able to migrate or interact with the medicinal product is difficult. In this case, the absence of toxicity of total extractables, demonstrated by a series of *in vitro* and/or *in vivo* tests, would complete the risk analysis and improve the control of the toxicological risk.

The samples used for toxicological tests are preferably obtained from the final formulation, but, when the active ingredient presents a specific toxicity, use of a placebo (vehicle without active ingredient) could be the only acceptable solution.

During the preliminary assessment, additional tests can be performed on total extractables, such as non-volatile residues (NVR), total organic carbon (TOC), which provide information on the quantity of substances extracted per dose administered, which can then be compared to an acceptable threshold, applicable for an individual unknown genotoxic extractable (TTC value under discussion).

The risk is also evaluated on the basis of the supplier's information, such as:

- the plastic family (polyester, polycarbonate, etc.), which provides information about the potential list of extractables,
- the declaration of the absence of alert compounds, identified as indicators of a possible carcinogenic-genotoxic activity.

Il faut cependant noter qu'une évaluation des extractibles totaux n'est pas suffisante pour les autorités réglementaires qui imposent de délivrer la liste des extractibles et relargables.

3.4. Utilisation des banques de données

Lorsqu'une modification du profil d'extractible ou de relargable est observée, et avant de décider d'une étude toxicologique expérimentale, une approche d'analyse des risques peut être réalisée sur les molécules dont le numéro CAS est connu. Partant de ce numéro, des banques de données toxicologiques ainsi que les banques de données bibliographiques internationales sont interrogées afin de compiler les données disponibles.

Le résultat de cette démarche est très variable ; certaines molécules ne sont pas répertoriées dans les banques de données alors que d'autres pourront générer des centaines de pages de réponses. Il est alors nécessaire d'extraire les données numériques les plus scientifiquement consistantes.

La plupart du temps, ces données sont des valeurs de type dose létale 50 % (DL50 ou NOEL). Alors que les valeurs NOEL peuvent être directement assimilées à des valeurs de dose sans effet nocif (DSENO), les valeurs de DL50 (50 % d'effet létal) ou de type LOEL doivent être pondérées afin de tenir compte de l'écart avec la dose ne présentant réellement pas d'effet toxique potentiel sur une population. Si elle est disponible, la valeur NOAEL ou LOEL sera largement préférée dans l'utilisation.

Le choix du facteur de pondération a fait et fait encore l'objet de nombreuses discussions. Dans la littérature, des valeurs de 10 à 50 000 ont été proposées selon les cas. Une valeur trop faible peut conduire à une sous-estimation du risque et à considérer comme sûrs des polymères douteux, alors qu'une valeur excessive, si elle protège le toxicologue, conduit implicitement toute molécule à l'exclusion.

De manière plus réaliste, des valeurs de 300 à 1 000 sont utilisées le plus souvent en fonction de la molécule et du niveau d'étude détaillée de la littérature qui a pu être réalisée. Toutefois, la DSENO n'est pas encore la valeur utilisable finale car il faut de nouveau pondérer de facteurs d'incertitude qui sont liés aux données utilisées et à leur application.

L'ISO 10993-17 et l'autosaisine Afsset (VTR, avril 2007) ont défini une liste de paramètres, dont la variabilité interspécies, la variabilité interindividuelle, la transposition de résultats des tests de toxicité aiguë en chronique, la transposition des modes d'administration, la qualité des données, la gravité des effets, qui permettent de définir un facteur d'incertitude global (FI) qui peut aller de 100 à plus de 10⁶.

Le rapport DSENO/FI permet d'obtenir la dose journalière admissible (DJA), exprimée en mg/kg/j, qui peut ensuite être rapportée à la masse moyenne d'un individu (en général 70 kg) pour définir la limite journalière acceptable pour l'extractible concerné, ou valeur toxicologique de référence (VTR). Si la quantité de l'extractible mesurée expérimentalement,

However, assessment based on total extractables is not sufficient for regulatory authorities, which require a documented list of extractables and leachables.

3.4. Use of databases

When a modification of the extractables or leachables profile is observed, and before deciding to perform an experimental toxicity study, a risk analysis approach can be performed on molecules for which the CAS registry number is known. The CAS number can be used to search toxicological databases and international literature databases in order to compile available data.

The results of this approach are very variable, as some molecules are not listed in databases, while others can generate hundreds of pages of responses. The most scientifically consistent numerical data must then be extracted.

These numerical data usually correspond to values such as lethal dose 50 % (LD50 or NOEL). While no observed effect level (NOEL) values can be directly linked to the no observed adverse effect level (NOAEL), lethal dose 50 % (LD50) or lowest observed effect level (LOEL) values must be weighted by the difference with the dose not really presenting any potential toxic effect in a population. When available, the NOAEL or LOEL value should be preferred.

The choice of weighting factor is still a subject of debate. Values ranging from 10 to 50,000, depending on the case, have been proposed in the literature. An excessively low value can lead to underestimation of the risk, resulting in doubtful polymers being considered to be safe, while an excessively high value, although it protects the toxicologist, implicitly leads to the exclusion of all molecules.

More realistically, values of 300 to 1,000 are generally used, depending on the molecule and the level of detail of the literature review performed. However, the NOAEL value cannot be used as the final value, as it must be weighted by uncertainty factors related to the data used and their application.

ISO 10993-17 and the Afsset investigation (VTR, April 2007) defined a list of parameters, including inter-species variability, inter-individual variability, transposition of acute-to-chronic toxicity test results, transposition of modes of administration, quality of data, severity of effects, that can be used to define a global uncertainty factor (UF) ranging from 100 to more than 10⁶.

The NOAEL/UF ratio provides the acceptable daily intake (ADI) expressed in mg/kg/day which can then be expressed in relation to the average mass of an individual (generally 70 kg) to define the acceptable daily limit for the extractable concerned or the toxicity reference value (TRV). If the experimentally measured quantity of extractable to which the user

à laquelle l'utilisateur est potentiellement exposé, dépasse cette VTR, voire s'en approche d'un facteur 1 à 10 selon les molécules ou les modes de calcul utilisés [35, 36], l'analyse de risque ne permet pas de statuer.

Dans ce cas une étude toxicologique expérimentale de la molécule s'impose, ce qui ne dispense pas de la réalisation d'une étude sur la toxicité globale des extractibles et relargables totaux dans la mesure où les interactions moléculaires peuvent conduire à des phénomènes additifs, voire de potentialisation des effets toxiques.

4. CHOIX DES TESTS TOXICOLOGIQUES EXPÉRIMENTAUX

Le fournisseur est susceptible d'apporter certains résultats de biocompatibilité. Cependant, il convient souvent de compléter ces tests en fonction du produit et des résultats d'extractibles et simulation.

4.1. Généralités

Le choix des tests toxicologiques doit reposer sur une approche scientifiquement fondée en réalisant des essais correspondant le plus étroitement possible aux conditions d'utilisation du matériel et aux voies d'exposition. Parallèlement, un certain nombre d'essais sont décrits dans les normes ISO, OCDE, USP ainsi que dans certaines pharmacopées (Pharmacopée japonaise en particulier). Ces essais peuvent être parfois appliqués sans modification aucune ; toutefois, très souvent il sera nécessaire d'adapter ces protocoles en essayant de rester au plus près des normes et du mode d'interaction du matériau avec les cellules et tissus concernés. Ainsi, même si l'ISO 10993-5 ne répertorie comme lignées cellulaires que des fibroblastes et des cellules rénales, en particulier dans le cas des matériaux implantables, le test de cytotoxicité devra être réalisé sur la ou les formes cellulaires réellement en contact, la biocompatibilité des matériaux pouvant changer totalement selon le mode d'interaction et la nature du tissu.

Certaines normes telles que celles de la Pharmacopée japonaise permettent d'évaluer non seulement la mort cellulaire, mais aussi la vitesse de croissance, et s'avèrent plus précises et plus sensibles.

La norme ISO 10993, constituée de vingt parties, est destinée à l'évaluation biologique des dispositifs médicaux. La partie 1 définit les tests à réaliser en fonction de la nature du contact avec le corps et de la durée du contact. Les autres parties traitent des essais (voir chapitre 10, normes ISO 10993).

L'USP décrit également des essais de réactivité biologique *in vitro* et *in vivo* permettant d'évaluer la toxicité des extractibles des plastiques et élastomères : <87> Biological reactivity tests *in vitro*, <88> Biological reactivity tests *in vivo*.

4.2. Essais de sensibilisation

Les seuls essais de sensibilisation (réaction allergique inflammatoire) complètement validés à ce jour

is potentially exposed exceeds the TRV, or is situated within a range of 1 to 10 times the TRV, depending on the molecule or the methods of calculation used [35, 36], risk analysis will not be sufficient.

In this case, an experimental toxicity study must be conducted on the molecule, in addition to the global toxicity study of total extractables and leachables, as molecular interactions can lead to additive phenomena or even potentiation of toxic effects.

4. CHOICE OF EXPERIMENTAL TOXICITY TESTS

The supplier can provide certain biocompatibility results. However, these tests often need to be completed by other tests depending on the product and results of extractables and simulation studies.

4.1. Introduction

The choice of toxicity tests must be based on a scientific approach by performing tests corresponding as closely as possible to the real conditions of use of the material and the routes of exposure. In parallel, a number of tests are described in ISO, OECD, USP standards and in certain pharmacopoeias (particularly the Japanese Pharmacopoeia). These tests can sometimes be applied without any modification. However, these protocols generally need to be adapted, while trying to remain as close as possible to standards and the mode of interaction of the material with the cells and tissues concerned. For example, although the only cell lines indicated by ISO 10993-5 are fibroblasts and renal cells, particularly in the case of implantable materials, cytotoxicity tests should be performed on the cells actually in contact, as the biocompatibility of materials can change considerably according to the mode of interaction and the type of tissue.

Some standards, such as those published in the Japanese Pharmacopoeia, can be used to evaluate not only cell death, but also cell growth rate and tend to be more precise and more sensitive.

ISO 10993, composed of twenty parts, describes biological evaluation of medical devices. Part 1 defines the tests to be performed depending on the type of contact with the body and the contact time. The other parts describe the various tests (see chapter 10, ISO 10993).

The USP also describes biological reactivity tests *in vitro* and *in vivo* to evaluate the toxicity of extractables from plastics and elastomers: <87> Biological reactivity tests *in vitro*, <88> Biological reactivity tests *in vivo*.

4.2. Sensitization tests

The only sensitization tests (inflammatory allergic reaction) completely validated at the present time are

sont tous des tests *in vivo*. Le test de référence reste le *Guinea pig maximization test* (GPMT), décrit en particulier dans l'ISO 10993-10. On trouve aussi le *local lymph node assay* (LLNA) réalisé chez la souris et enfin, mais d'intérêt plus limité dans le cas des formes à usage parentéral, le *human patch test* (HPT). Depuis la révision de la directive européenne 76/768/EEC appliquée à partir de 2009, et sous la pression de l'industrie cosmétique pour laquelle tous les tests *in vivo* sont prohibés, des nouveaux modèles alternatifs *in vitro* sont en cours de développement. Ces modèles combinent une série de mesures (capacité d'hapténation des molécules, induction de cytokines et de marqueurs de mort cellulaire, etc.) et parfois une approche *in silico* de type « *quantitative structure activity relationships* » (QSAR). Bien que n'étant pas destinés aux produits pharmaceutiques et en particulier à l'évaluation des réactions de sensibilisation systémiques, ces tests peuvent permettre de réaliser un criblage pré-réglementaire dans le cadre du développement d'un nouveau matériau.

4.3. Le potentiel pyrogène

Le potentiel pyrogène est à l'origine la mesure de la capacité d'une molécule à induire une réaction d'hyperthermie. Cette mesure est un paramètre à ne pas négliger dans le cas de nouveaux matériaux pour usage parentéral. Le test de référence est le *rabbit pyrogen test* (USP), réalisé *in vivo* chez le lapin. D'une réalisation délicate, il lui a été substitué depuis longtemps le *limulus amoebocyte lysate test* (test LAL). Toutefois, il est essentiel de garder à l'esprit que ce test ne permet que la détection d'endotoxines bactériennes et non celle de la plupart des pyrogènes d'origine artificielle. Le test d'activation monocyttaire (test MAT, Pharmacopée européenne, chap. 2.6.30), basé sur la mesure de cytokines, est bien mieux adapté à la détection des pyrogènes potentiellement libérés par des polymères synthétiques, mais sa mise en œuvre reste complexe compte tenu du degré de liberté laissé à l'utilisateur [37].

4.4. Les tests d'irritation

Les tests d'irritation ou de réaction intradermique, bien que décrits *in vivo* dans les normes ISO ou OCDE, peuvent aujourd'hui être conduits selon des approches *in vitro* validées par l'ECVAM. Dans les phases de développement, ces essais peuvent être réalisés sur fibroblastes en culture selon l'ISO 10993-5 car le coût des modèles tissulaires (épidermes) reconstitués reste encore relativement élevé. Les indicateurs d'irritation sont en général des tests de mort cellulaire tels que le test MTT, utilisant la conversion de sels de tétrazolium en formazan sous l'effet de la respiration mitochondriale.

4.5. Les études de toxicité aiguë

Les études de toxicité systémique aiguë sont classiquement assimilées à l'évaluation de la dose létale

all *in vivo* tests. The reference test remains the Guinea pig maximization test (GPMT), described, in particular, in ISO 10993-10, which also describes the local lymph node assay (LLNA) performed in mice and finally, but of more limited value for parenteral preparations, the human test patch (HPT). Since amendment of European Directive 76/768/EEC that entered into force in 2009, and in response to pressure from the cosmetic industry, in which all *in vivo* tests are banned, new alternative *in vitro* models are currently under development. These models comprise a series of tests (haptentation capacity of molecules, induction of cytokines and markers of cell death, etc.) and sometimes an *in silico* approach such as quantitative structure activity relationships (QSAR). Although not originally intended for pharmaceuticals, particularly for evaluation of systemic sensitization reactions, these tests can be used for pre-regulatory screening in the context of development of a new material.

4.3. Pyrogenic potential

Pyrogenic potential is originally measurement of the capacity of a molecule to induce a hyperthermia reaction. This parameter must be taken into account in the development of new materials for parenteral use. The reference test is the rabbit pyrogen test (USP) performed *in vivo* in rabbits. This test is difficult to perform and has been replaced for a long time by the limulus amoebocyte lysate (LAL) test. However, it must be kept in mind that this test only allows the detection of bacterial endotoxins, but does not detect most of the artificial pyrogens. The monocyte activation test (MAT, European Pharmacopoeia 2.6.30), based on measurement of cytokines, is much more suitable for the detection of pyrogens potentially released by synthetic polymers, but it is complicated to perform in view of the degree of freedom left to the user [38].

4.4. Irritation tests

Irritation tests or intradermal reaction, although described *in vivo* in ISO or OECD standards, can now be performed according to *in vitro* approaches validated by the ECVAM. During development phases, these tests can be performed on fibroblast cultures according to ISO 10993-5, as the cost of reconstituted tissue models (epidermis) still remains relatively high. Indicators of irritation are generally cell death tests, such as the MTT test using conversion of tetrazolium salts into formazan in response to mitochondrial respiration.

4.5. Acute toxicity studies

Acute systemic toxicity studies classically involve evaluation of the lethal dose 50 % (LD50) in rodents.

50 % (DL50) sur rongeurs. Depuis 2002, les tests classiques de DL50 tels que décrits dans la norme OCDE TG401 sont considérés comme obsolètes et remplacés par des méthodes substitutives décrites dans les normes TG420 et apparentées. Il est aussi préférable, tant pour des raisons de coût que de délais, de passer par des modèles dits « alternatifs » dans les études de développement. Différents modèles alternatifs ont été développés, comme en particulier le nématode *Caenorhabditis elegans*, aujourd'hui considéré comme un équivalent du modèle murin pour l'étude de la toxicité aiguë [38, 39].

4.6. Les études de génotoxicité

Les études de génotoxicité visent à évaluer les effets clastogènes (induction de lésions chromosomiques qualitatives), aneugènes (induction de lésions chromosomiques quantitatives) et carcinogènes (effets cancérogènes ou cancérigènes). Pour cela, en première intention différents tests rapides sur micro-organismes, dont les tests d'Ames sur *Salmonella typhimurium*, SOS chromotests sur *Escherichia coli* ou Mutatox/Microtox sur *Vibrio fischeri*, peuvent être utilisés. Toutefois, une confirmation de l'absence d'effet génotoxique *in vitro* sur cellule eucaryote est indispensable. Ces tests de type micronoyaux, échanges de chromatides sœurs, synthèse non programmée de l'ADN ou de type comètes, sont décrits dans les normes OCDE 474 à 486. Dans le cas de polymères implantables, des études long terme de cancérogénicité (OCDE 451 et 453, ICH S2R1...) doivent être réalisées *in vivo* en respectant le mode d'implantation et les types de tissus en contact dans l'utilisation finale du matériau.

4.7. Évaluation de l'hémocompatibilité

L'évaluation de l'hémocompatibilité est décrite en détails selon les durées et les modes de contact dans la norme ISO 10993-4.

Les tests toxicologiques doivent donc être définis à la fois en fonction du type de conditionnement (primaire ou non), du temps d'interaction avec le matériau, du mode d'interaction et de la posologie à laquelle le médicament sera utilisé, conditionnant de fait la durée totale d'exposition aux relargages contenus. Les informations portant sur les extractibles totaux sont inhérentes au matériau et sont censées relever de la responsabilité du fournisseur. En revanche, la nature des extractibles étant liée à celle du contenu, seul l'utilisateur final sera en mesure de qualifier le produit dans son type d'application. L'ensemble de ces données a été résumé dans le *tableau 11*.

5. LOGIGRAMME

Les différentes étapes à considérer lors de l'étude de la compatibilité d'un matériau avec un injectable sont ainsi résumées dans la *figure 2*.

La première étape consiste à réaliser une analyse

However, since 2002, classical LD50 tests, such as those described in OECD standard TG401, are considered to be obsolete and have been replaced by the substitute methods described in TG420 and related standards. It is also preferable, both in terms of cost and time, to use so-called alternative models in development studies. Various alternative models have been developed, particularly the *Caenorhabditis elegans* nematode, now considered to be equivalent to the murine model for acute toxicity studies [38, 39].

4.6. Genotoxicity studies

Genotoxicity studies are designed to evaluate clastogenic effects (induction of qualitative chromosomal lesions), aneugenic effects (induction of quantitative chromosomal lesions) and carcinogenic effects. Various first-line rapid tests on microorganisms, including Ames' test on *Salmonella typhimurium*, SOS chromotests on *Escherichia coli* or Mutatox/Microtox on *Vibrio fischeri*, can be used. However, confirmation of the absence of *in vitro* genotoxic effects on eukaryotic cells is essential. These tests, corresponding to micronucleus tests, sister chromatid exchange tests, unprogrammed DNA synthesis test or comet test, are described in OECD standards 474 to 486. Long-term *in vivo* carcinogenicity studies (OECD 451 and 453, ICH S2R1, etc.) must be performed on implantable polymers, taking into account the mode of implantation and the types of tissues in contact with the material under real use conditions.

4.7. Evaluation of haemocompatibility

Evaluation of haemocompatibility is described in detail according to durations and modes of contact in ISO 10993-4.

Toxicological tests must therefore be defined both as a function of the type of packaging (primary or non-primary), interaction time with the material, mode of interaction and the dosage at which the medicinal product will be used, which consequently determines the total exposure time to leachables present in the material. Information on total extractables is inherent to the material and therefore corresponds to the supplier's responsibility. However, as the nature of extractables is related to the nature of the content, only the final user is able to qualify the product for the specific type of application. All these data are summarized in *Table 11*.

5. FLOW-CHART

The various steps to be considered during the compatibility study of a material with a parenteral preparation are summarized in *Figure 2*.

The first step consists of performing an interac-

Tableau 11. Analyse de risque et tests toxicologiques.

	Essais initiaux d'évaluation à prendre en considération							Essais complémentaires d'évaluation à prendre en considération		
	Temps de contact matériau*	Durée de traitement**	Cytotoxicité	Sensibilisation	Irritation ou réaction aiguë	Toxicité systémique aiguë	Hémo-compatibilité	Muta-génicité	Toxicité chronique	Cancérogénicité
contenant primaire final ^a	3	A	X	X	X	X	X			
		B	X	X	X	X	X		X	
		C	X	X	X	X	X	X		X
conditionnement secondaire ^b	3	A	X	X	X			X		
		B	X	X	X			X		
		C	X	X	X			X		
conditionnement intermédiaire (ex. : contenant en plastique)	1	A	X	X	X	X	X			
		B	X	X	X	X	X		X	
		C	X	X	X	X	X		X	
	2	A	X	X	X	X	X	X		
		B	X	X	X	X	X	X		X
		C	X	X	X	X	X	X		X
	3	A	X	X	X	X	X	X		
		B	X	X	X	X	X	X		
		C	X	X	X	X	X	X		
matériau en contact pendant le process (ex. : filtres, tuyaux de transfert, connecteurs...)	1	A	X	X	X	X	X			
		B	X	X	X	X	X			
		C	X	X	X	X	X			
	2	A	X	X	X	X	X	X		
		B	X	X	X	X	X	X		
		C	X	X	X	X	X	X		

1. < 24 heures. 2. Entre 24 heures et 30 jours. 3. > 30 jours. A. Dose unique. B. Dose répétée (24 h à 30 j). C. Traitement chronique (> 30 j).

^aExemples : poche, flacon, bouchon, cartouche, étiquette avec encre.

^bExemples : absorbeur, indicateur d'oxygène, suremballage.

Table 11. Risk analysis and toxicological tests.

	Material contact time*	Duration of treatment**	Initial evaluation tests to be considered							Complementary evaluation tests to be considered		
			Cytotoxicity	Sensitization	Irritation or intradermal reaction	Acute systemic toxicity	Hemo-compatibility	Muta-genicity	Chronic toxicity	Carcino-genicity		
final primary container ^a	3	A	X	X	X	X	X	X				
		B	X	X	X	X	X	X			X	
		C	X	X	X	X	X	X			X	X
secondary packaging ^b	3	A	X							X	X	
		B	X							X	X	
		C	X								X	X
intermediate packaging (e.g.: plastic container)	1	A	X	X	X	X	X	X	X	X	X	
		B	X	X	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X	X	X
	2	A	X	X	X	X	X	X	X	X	X	
		B	X	X	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X	X	X
	3	A	X	X	X	X	X	X	X	X	X	
		B	X	X	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X	X	X
material in contact during the process (e.g.: filters, transfer pipes, connectors, etc)	1	A	X	X	X	X	X	X	X	X		
		B	X	X	X	X	X	X	X	X		
		C	X	X	X	X	X	X	X	X		
	2	A	X	X	X	X	X	X	X	X		
		B	X	X	X	X	X	X	X	X		
		C	X	X	X	X	X	X	X	X	X	

1. < 24 hours. 2. Between 24 hours and 30 days. 3. > 30 days. A. Single dose. B. Repeated dose (24 h to 30 days). C. Chronic treatment (> 30 days).

^aE.g.: bag, bottle, stopper, cartridge, label with ink.

^bE.g.: desiccant, oxygen indicator, overwrap.

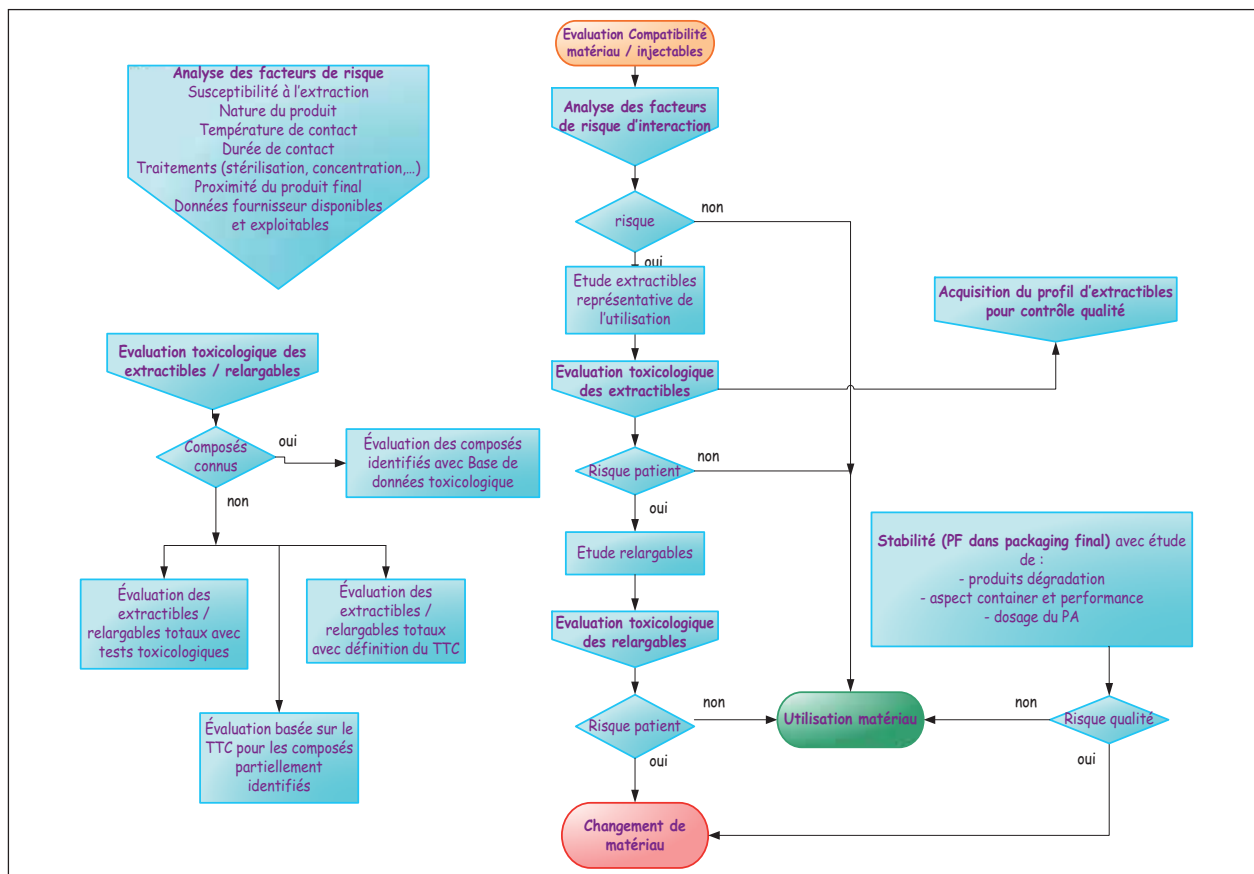


Figure 2. Méthodologie des études de compatibilité pour les injectables.

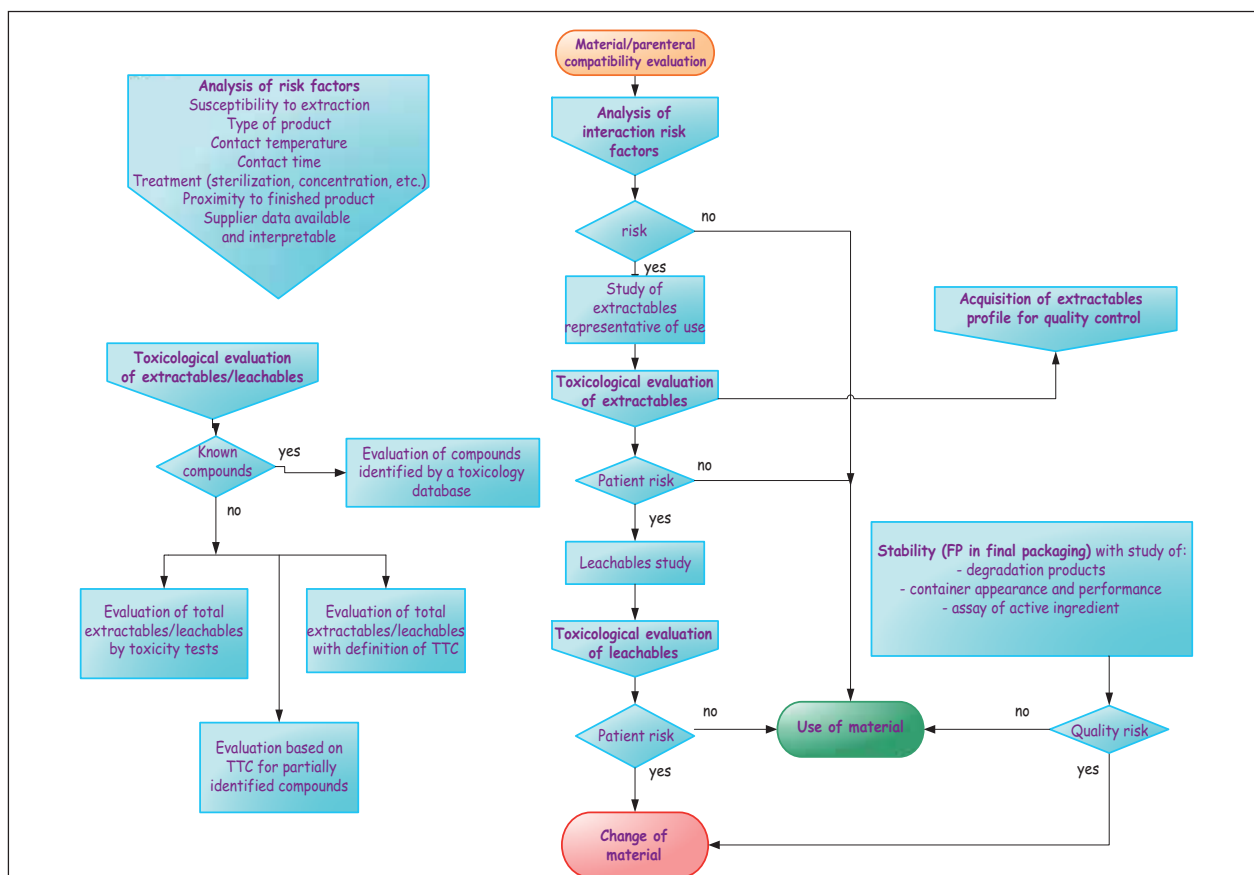


Figure 2. Methodology of compatibility study for injectables.

de risque d'interaction qui prend en compte tous les facteurs susceptibles d'intervenir à ce niveau. Les données fournisseur doivent aussi être considérées afin de diminuer le risque obtenu.

Les conclusions de cette analyse de risque initiale conduisent ou non à la mise en place d'une étude d'extractible/simulation, représentative de l'utilisation du matériau en question et une évaluation toxicologique des extractibles obtenus.

Lorsqu'un risque patient a été identifié, une étude de relargable (en conditions réelles) est dès lors nécessaire pour évaluer le risque réellement présent pour le patient.

Cette évaluation doit être réalisée en parallèle avec l'évaluation des données de stabilité ou de validation (selon qu'il s'agit d'un article de conditionnement ou un équipement de fabrication) pour estimer le risque qualité. Elle permet aussi de définir les tests à réaliser en routine pour le contrôle qualité.

L'évaluation toxicologique réalisée aux différents stades peut utiliser les bases de données toxicologiques ou les limites admissibles fixées (SCT), selon l'identification ou non des composés ayant migré.

V CONTRÔLE QUALITÉ

Une fois le matériel qualifié, il convient d'assurer son suivi tout au long de sa vie. Un plan de contrôle qualité doit être établi.

Le contrôle qualité intervient sur les différents matériaux en contact avec le produit en cours de fabrication ou pour son stockage. En effet, après la qualification initiale, il est indispensable de contrôler en routine la qualité des différentes parties du packaging.

Des tests à libération de chaque lot doivent être réalisés ainsi que d'autres tests à intervalles réguliers. La stratégie est généralement établie selon l'analyse de risque préalablement établie intégrant les connaissances disponibles sur le matériau, sa compatibilité avec le produit pharmaceutique et les types de contrats fournisseurs.

Le fournisseur est responsable du suivi de la qualité des matériaux utilisés, quel que soit le type de ces matériaux (résines/granulés, pièces injectées, conditionnement vide, assemblage complet) et doit pouvoir fournir des certificats d'analyses selon les exigences du client. Si le fournisseur est dans l'incapacité de réaliser les analyses, il revient au client de contrôler les matériaux réceptionnés, afin de vérifier la constance de ces matériaux, via le contrôle qualité.

Pour chaque lot de composant, les tests d'intégrité et paramètres physiques, l'aspect et un test d'identification (exemple : IR) sont le minimum requis, comme décrit dans le *tableau 12*.

Les contrôles à réception ne comportent pas de tests relatifs à la compatibilité. Un suivi périodique devrait être mis en place, à une fréquence définie selon la politique de chaque entreprise, avec des tests simples qui permettent de comparer les lots reçus à ceux utilisés pour la qualification initiale (*tableau 13*).

tion risk analysis, which takes into account all factors likely to be involved at this level. Supplier data must also be considered in order to minimize the risk.

Based on the conclusions of this initial risk analysis, an extractables/simulation study, representative of the use of the material concerned, and toxicological evaluation of the extractables obtained may need to be performed.

When a patient risk has been identified, a leachables study (under real conditions) is necessary to evaluate the effective risk for the patient.

This evaluation must be performed in parallel with evaluation of stability or validation data (depending on whether the material is a packaging material or manufacturing equipment) to estimate the quality risk. It also indicates the tests that must be performed routinely for quality control.

The toxicological evaluation performed at the various stages can use toxicology databases or safety concern thresholds (SCT), depending on whether or not the compounds that have migrated have been identified.

V QUALITY CONTROL

After qualifying the material, this material must be monitored throughout its life. A quality control plan must be established.

Quality control is performed on the various materials in contact with the product during manufacture or during storage, as, following initial qualification, it is essential to routinely control the quality of the various parts of the packaging.

Release tests and periodic testing must be performed on each batch. The quality control strategy is generally established on the basis of the previously defined risk analysis, integrating all available knowledge on the material, its compatibility with the pharmaceutical product and types of supplier contracts.

The supplier is responsible for quality control of the material used, regardless of the type of material (resins/granules, extruded parts, empty packaging, complete assembly) and must be able to provide certificates of analysis according to the customer's requirements. When the supplier is unable to perform analyses, the customer must perform control tests on the materials received in order to verify the consistency of these materials by quality control.

The minimum requirements for each batch of ingredient are integrity tests and physical parameters, appearance and an identification test (e.g.: IR), as described in *Table 12*.

In-coming quality control tests do not comprise compatibility tests. Periodic testing should be performed at a frequency defined according to each company's policy, based on the use of simple tests to compare the batches received with those used for the initial qualification (*Table 13*). An extractables

Tableau 12. Tests à libération pour chaque lot de matériaux ou éléments de conditionnement.

Table 12. Release tests for each batch of material or packaging.

Matériau/conditionnement / Material/packaging	Tests
Résine/Resin	Tests Pharmacopée (Ph. Eur et/ou USP) ou monographie interne Pharmacopoeia tests (Ph Eur and/or USP) or in-house monograph
Pièces injectées (bouchons, port système...) Extruded parts (stoppers, port system, etc.)	Contrôle visuel et dimensionnel/Visual inspection and dimensions Intégrité/Integrity Identification (ex. : IR...)
Emballage vide (poche, flacon seringue) Empty packaging (bag, vial, syringe)	Contrôle visuel et dimensionnel/Visual inspection and dimensions Particules/Particles Intégrité/Integrity Identification (ex. : IR...) Résistance des soudures/Sealing test
Assemblage complet imprimé Printed complete assembly	Contrôle visuel/Visual control Résistance des soudures/Sealing test

Tableau 13. Suivi de la qualité. Tests sur les matériaux selon les objectifs du contrôle qualité.

Table 13. Quality control. Tests on materials according to the objectives of quality control.

Matériau/conditionnement / Material/packaging	Tests (fréquence à définir par chaque entreprise) (frequency of tests to define by each company)
Résine/Resin	NA
Pièces injectées (bouchons, port système...) Extruded parts (stoppers, port system, etc.)	Test Pharmacopée (Ph. Eur. et/ou USP) ou monographie interne Pharmacopoeia tests (Ph Eur and/or USP) or in-house monograph Bouchons/Stoppers : Ph. Eur 3.1.9 ; USP <381> Plastiques : si applicable/Plastics: if applicable : 3.1.3 ; 3.1.4 ; 3.1.5 ; 3.1.6 ; 3.1.7 ; USP <661> Tests microbiologiques (LAL, Bioburden). Stérilité Microbiological tests (LAL, Bioburden). Sterility Cytotoxicité/Cytotoxicity Résidus non volatiles/Non-volatile residues
Emballage vide (poche, flacon seringue) Empty packaging (bag, vial, syringe)	Test Pharmacopée et/ou USP : 3.2.2.1, <661> ou monographie interne Pharmacopoeia test and/or USP: Ph Eur 3.2.2.1, USP <661> or in-house monograph Tests microbiologiques (LAL, Bioburden). Stérilité Microbiological tests (LAL, Bioburden). Sterility Cytotoxicité/Cytotoxicity Résidus non volatiles/Non-volatile residues
Assemblage complet imprimé/Printed complete assembly	NA

Un profil d'extractibles est d'ailleurs recommandé dans la directive FDA [7] pour les produits injectables et à usage ophtalmique.

Les caractéristiques physiques, microbiologiques (LAL et charge bactérienne) mais aussi chimiques doivent être suivies lors de ces contrôles de routine. Il est important de vérifier à intervalles réguliers que les composants sont conformes aux pharmacopées applicables (Ph. Eur. ou USP) ou à une monographie interne. Par exemple, pour les contenants primaires on vérifiera que les résultats sont conformes à la monographie Ph. Eur. 3.2.2.1 ou USP <661> ; pour les bouchons les monographies Ph. Eur. 3.1.9 et USP <381> sont applicables. La fréquence de ces tests dépendra du nombre de lots reçus annuellement, de l'analyse de risque et de la politique qualité de l'entreprise.

La quantité de résidu non volatile peut être un bon indicateur de la qualité du packaging. Si cette dernière augmente de façon significative (par exemple, résultat supérieur de 10 % à la qualification initiale), un profil d'extractibles devrait être réalisé et comparé à celui d'origine. Un test de cytotoxicité une fois par an peut également être un garant de qualité du packaging.

Un test d'intégrité est également recommandé sur

profile is also recommended in FDA guidelines [7] for parenteral and ophthalmic preparations.

Physical, microbiological (LAL and bioburden), as well as chemical characteristics must be monitored during these routine control tests. It is important to ensure, at regular intervals, that the components comply with the applicable Pharmacopoeias (Ph. Eur. or USP) or an in-house monograph. For example, primary containers must comply with Ph. Eur. 3.2.2.1 or USP <661> and stoppers must comply with Ph. Eur. 3.1.9 and USP <381>. The frequency of testing depends on the number of batches received each year, risk analysis and the company's quality policy.

The quantity of non-volatile residues can be a good indicator of the quality of the packaging. When the quantity of non-volatile residues increases significantly (for example, result 10 % higher than at the initial qualification), an extractables profile should be performed and compared to the original profile. An annual cytotoxicity test can also be used to ensure the quality of the packaging

An integrity test on the filled and sterilized final

l'assemblage final rempli et stérilisé au minimum une fois par an.

VI CONCLUSION

L'analyse de risque permet de cibler les informations et études nécessaires pour évaluer la qualité, la sécurité et l'efficacité du produit injectable selon les textes en vigueur. Sa pertinence est étroitement liée aux informations mises à disposition par le fournisseur du matériau constituant le packaging ou utilisé en cours de fabrication. La constance de la composition chimique des matériaux devra être vérifiée périodiquement pour ne pas invalider les études réalisées.

La mise en œuvre des études est complexe sur le plan analytique, consommatrice de ressources et présente des défis scientifiques (larges volumes parentéraux et seuils analytiques associés par exemple). Par ailleurs, l'exploitation des résultats analytiques se heurte à la difficulté de déterminer des limites acceptables pour le patient sur la base des données toxicologiques bibliographiques (choix ou limitation des données disponibles), et aux difficultés d'interprétation des tests toxicologiques.

De plus, on note une absence de limites réglementaires harmonisées et spécifiques aux extractibles et relargables.

Cependant, ces études bénéficient des progrès scientifiques, notamment dans les systèmes de détection analytique et du développement des expertises dans ce domaine.

La multitude des groupes de travail incluant des autorités de santé et travaillant activement sur ce sujet témoigne de la nécessité et de la volonté d'aboutir à des recommandations applicables pour les produits parentéraux.

assembly is also recommended at least annually.

VI CONCLUSION

Risk analysis helps to define the information and studies necessary to evaluate the quality, safety and efficacy of the parenteral preparation according to current regulations. The relevance of risk analysis is closely related to the information provided by the supplier of the material constituting the packaging or used during manufacture. The consistency of the chemical composition of the material should be checked periodically to ensure the validity of the studies performed.

These studies are complex in terms of analytical techniques, resource consuming and represent a scientific challenge (for example large volume parenterals and associated analytical thresholds). Application of the analytical results can also be complicated by the difficulty of defining acceptable limits for the patient on the basis of published toxicological data (choice of data or limited data available), and the difficulties of interpretation of toxicity test results.

A further complication is the absence of harmonized regulatory limits specific for extractables and leachables.

However, these studies have been facilitated by scientific progress especially related to analytical detection systems and the development of expertise in this field.

The large number of task forces, including health authorities, actively working on this subject illustrate the need and the determination to define guidelines applicable recommendations for parenteral preparations.

Annexe - Composés courants trouvés dans les polymères et élastomères et techniques d'analyse Appendix - Compounds commonly found in polymers and elastomers and analytical techniques

Catégorie/Category	Composés/Compounds	Technique
Composés volatiles Volatile compounds	Solvants, résidus de synthèse des polymères, monomères/Solvents, synthetic residues of polymers, monomers Ex. : aromatic (benzene, toluene, xylene...), aldehydes (butanal, hexanal, 2-methyl-2-propanal...), alcohols (ethanol, 2-methyl-2-propanol...), ketones (acetone, 2-butanone, methylethylketone...), acids (propionic acid...), esters (2-ethyl ester...), alkanes	GC Headspace, SPME GC-MS/GC-FID
Composés semi-volatiles Semi-volatile compounds	Lubrifiants, additifs, anti-oxydants, produits de dégradation des polymères/Lubricants, additives, antioxidants, polymer degradation products Ex. : butylated hydroxytoluene, phthalates, oleamide, erucamide, Irgafos 168, Irganox 1076, 1,3-di-ter-butylbenzene, 2,4-bis-(1,1-dimethylethyl)-phenol, 3,5-di-ter-4-hydroxybenzaldehyde, caprolactam, butyrolactone, 4-butoxy-1-butanol	LI/GC-MS/GC-FID
Composés non volatiles Non volatile compounds	Antioxydants, agents nucléants, acides gras, résines, stabilisants UV/Antioxidant, nucleants, fatty acids, resins, UV stabilizers Ex. : butylated hydroxytoluene, Irganox 1010, Irganox 1330, Irganox 1076, Irganox 3114, Irganox P5800, Irganox P5802, Hostonox O3, oleamide, erucamide, Irgafos 168, Irgafos P-EPQ, Weston 618	LC-MS/LC-PDA/LC-UV
Composés inorganiques Inorganic compounds	Ag, Al, Ba, Ca, Cd, Co, Cr, Cu, Fe, In, K, Li, Mg, Mn, Na, Ni, Pb, Si, Sr, Ti, Zn	ICP-AES/ICP-MS, IC
Pigments	Carbon black, Pigment yellow, Pigment red, Pigment blue...	UV



Glossaire/Glossary

Extractibles : espèces chimiques extraites du contenant à l'aide d'un solvant approprié, dans des conditions extrêmes de température et de durée d'extraction.

Extractables: chemical compounds extracted from the container using an appropriate solvent under exaggerated conditions of time and temperature

Relargables : substances chimiques qui peuvent migrer du contenant vers le contenu dans les conditions normales d'utilisation ou pendant la durée de validité du produit.

Leachables: chemical compounds that migrate from the container to the content under normal conditions of use or during the shelf-life of the product.

Abréviations/Abbreviations

AET : analytical evaluation threshold.

Afsset : Agence française de sécurité sanitaire de l'environnement et du travail (réorganisée au sein de l'Anses, Agence nationale de sécurité sanitaire de l'alimentation)

AIISI : American Iron and Steel Institute

AMDEC : analyse des modes de défaillance, de leurs effets et de leur criticité

ANP : atrial natriuretic peptide/peptide natriurétique auriculaire

BPSA : Bio-Process Systems Alliance (www.bpsalliance.org)

BSE/TSE : bovine spongiform encephalopathy/transmissible spongiform encephalopathy

CAS : Chemical Abstracts Service

CFR : Code of Federal Regulations

DSENO : dose sans effet nocif

DL50 : dose létale 50 %

ECVAM : European Centre for the Validation of Alternative Methods

ELSIE : Extractables and Leachables Safety Information Exchange (www.elsiedata.org)

EMA : European Medicines Agency

EU : European Union

EVA : ethylene-vinyl acetate

EVOH : ethylene- vinyl alcool

GH : growth hormone/hormone de croissance

GMP: good manufacturing practices

GPMT : Guinea pig maximization test

HPT : human patch test

IA : intra-artérielle

ICH : International Conference on Harmonisation

ICCVAM: Interagency Coordinating Committee on the Validation of Alternative Methods

ID : intradermique

IM : intramusculaire

IR : infrarouge

ISO : International Organization for Standardization

IV : intraveineuse

LAL: limulus amoebocyte lysate test

LOEL: lower observed effect level

LLNA: local lymph node assay

MAT: monocytes activation test

MTT : bromure de 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium

NICEATM: National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods

NOEL : no observed effect level

OCDE/OECD : Organisation de coopération et de développement économiques/Organisation for Economic Co-operation and Development

OINDP: orally inhaled and nasal drug products

PA : polyamides

PE : polyéthylène

PET : polyéthylène téréphtalate

JP : Japanese Pharmacopoeia

Ph. Eur : Pharmacopée européenne

PO : per os (voie entérale orale)

PP : polypropylène

PQRI : Product Quality Research Institute (www.pqri.org)

PVC : polychlorure de vinyle

QSAR : quantitative structure activity relationships

QT : qualification threshold

SC : sous-cutanée

SCT : safety concern threshold

TTC : threshold of toxicological concern

USP : United States Pharmacopoeia

UV : ultraviolet

VTR : valeurs toxicologiques de référence

REACH : Registration, Evaluation, Authorization of Chemicals

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- USP <51> Antimicrobial preservatives - Effectiveness.

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- USP<381> Elastomeric Closures for Injection.

- USP<85> Bacterial Endotoxins Test.

- USP<87> Biological reactivity tests, In Vitro.

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- USP<151> Pyrogen Test.

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- USP<661> Containers-plastics.

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- ISO 10993- Partie 17, Établissement des limites admissibles des substances relargables.
- ISO 10993- Partie 18, Caractérisation chimique des matériaux.
- ISO 10993- Partie 19, Caractérisation physicochimique, morphologique et topographique des matériaux [Spécification technique].
- ISO 10993- Partie 20, Principes et méthodes relatifs aux essais d'immunotoxicologie des dispositifs médicaux [Spécification technique].

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regulatory review

The current review period has seen a number of changes in the regulation of medicines and regulatory guidance in the EU, International markets and the USA

USA

Food and Drug Administration (FDA)

Drug Supply Chain Security Act (DSCSA) implementation: identification of suspect product and notification

A trading partner that determines a product in its possession or control as an illegitimate product as defined by section 581(8) of the Federal Food, Drug, and Cosmetic (FD&C) Act, must notify the FDA and certain immediate trading partners under section 582 of the FD&C Act (21 U.S.C. 360eee-1), as added by the DSCSA. This guidance identifies specific scenarios that could significantly increase the risk of a suspect product entering the pharmaceutical distribution supply chain; provides recommendations on how trading partners can identify a product and determine whether a product is a suspect product as soon as practicable; and sets forth the process by which trading partners should notify the FDA of illegitimate product or products with a high risk of illegitimacy, and how they must terminate the notifications, in consultation with the FDA.

The portion of this guidance that describes when manufacturers should notify the FDA if there is a high risk that a product is illegitimate is being distributed for comment purposes only.

Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product – Guidance for Industry

This guidance is intended to assist sponsors with the design and use of clinical pharmacology studies to support a decision that a proposed

therapeutic biological product is biosimilar to its reference product. This guidance pertains to those products – such as therapeutic biological products – for which pharmacokinetic and pharmacodynamic data are needed to support a demonstration of biosimilarity. Specifically, the guidance discusses some of the overarching concepts related to clinical pharmacology testing for biosimilar products, approaches for developing the appropriate clinical pharmacology database, and the utility of modelling and simulation for designing clinical trials.

FDA improves foreign inspection program/needs to assess the effectiveness/ staffing of foreign offices

The USA Government Accountability Office reports that the FDA has increased its foreign drug inspections and enhanced its ability to prioritise drug establishments for inspection. The number of foreign inspections has consistently increased each year since fiscal year 2009. Beginning in fiscal year 2015, the FDA conducted more foreign than domestic inspections. The FDA has also improved the accuracy and completeness of information on its catalog of drug establishments subject to inspection. It has also reduced its catalog of drug establishments with no inspection history to 33% of foreign establishments, compared to 64% in 2010. However, the number of such establishments remains large, at almost 1000 of the approximately 3000 foreign establishments. The FDA plans to inspect all of these establishments over the next 3 years.

Principal recommendations of the report are that the Commissioner of the FDA should:

- Assess the effectiveness of its foreign offices' contributions by systematically tracking information to measure whether the offices' activities specifically contribute to drug safety-related outcomes, such as

inspections, import alerts, and warning letters.

- Establish goals to achieve the appropriate staffing level for its foreign offices, which would include separating foreign office vacancies from the Office of International Programs-wide vacancy rate, and setting goals by position type.

Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Q&A

The FDA has now published these Q&A from the International Council for Harmonisation (ICH) Implementation Working Group (IWG) on development and manufacture of chemical entities and biotechnological/biological drug substances as a draft guidance.

New and revised draft guidances that Center for Drug Evaluation and Research (CDER) is planning to publish during calendar year 2017

The CDER has published this list of guidances that it intends to publish in calendar year 2017. There are 11 such guidances in the pharmaceutical quality/chemistry, manufacturing and control section; four in pharmaceutical quality/manufacturing standards (current good manufacturing practice (CGMP)); 13 in the generics section; and two in the biosimilarity section.

FDA ban on powdered medical gloves

The FDA issued a Final Rule banning all powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating surgical gloves intended for use by humans. The ban also applies to gloves used in the practice of veterinary medicine. This ban is effective 18 January 2017 for any devices intended for use by humans that are in commercial distribution and for any devices already sold to the ultimate user. This means that



powdered surgeon's gloves, powdered patient examination gloves, and absorbable powder for lubricating surgical gloves that have already been sold to or are already in the possession of end users, including veterinary clinics and animal surgical centres, are subject to the ban. The FDA advises stakeholders and institutions to dispose of pre-existing supplies of powdered medical gloves.

Nonproprietary Naming of Biological Products – Guidance for Industry

This guidance describes the FDA's current thinking on the need for biological products licensed under the Public Health Service (PHS) Act to bear a non-proprietary name that includes an FDA-designated suffix. Under this naming convention, the non-proprietary name designated for each originator biological product, related biological product, and biosimilar product will be a proper name that is a combination of the core name and a distinguishing suffix that is devoid of meaning and composed of four lower case letters. The suffix format described in this guidance is applicable to originator biological products, related biological products, and biosimilar products previously licensed and newly licensed under section 351(a) or 351(k) of the PHS Act. The FDA is continuing to consider the appropriate suffix format for interchangeable products.

Proposed New United States Pharmacopeia (USP) General Chapter <1220> The Analytical Procedure Lifecycle

An analytical procedure must be demonstrated to be fit for its intended purpose. It is useful to consider the entire lifecycle of an analytical procedure, i.e. its design and development, qualification, and continued verification. The current concepts of validation, verification, and transfer of procedures address portions of the lifecycle but do not consider it holistically. The purpose of this proposed new chapter is to more fully address the entire procedure

lifecycle and define concepts that may be useful. This approach is consistent with the concept of quality by design as described in ICH Q8-R2, Q9, Q10 and Q11. The lifecycle approach can potentially be applied to all procedures, although the level of effort should be consistent with the complexity and criticality of the procedure.

USP <1058> Analytical Instrument Qualification

This revised draft takes into account comments provided to the USP on the previous version.

A large variety of analytical instruments, ranging from a simple apparatus to complex computerised systems, is used in the pharmaceutical industry to acquire data that will help ensure that products meet their specifications. Many of these instruments combine a metrological function with software control. There are many ways of demonstrating that an instrument is qualified and under control, and these can include qualification, calibration, validation and maintenance. In order to ensure "fitness for purpose", an integrated approach, based upon a risk assessment, is recommended. For the purposes of this chapter, the term "instrument" includes any apparatus, equipment, instrument or instrument system used in the laboratory.

This chapter provides a scientific approach for carrying out an analytical instrument qualification; it is left to each laboratory to justify and document their specific approaches. The instrument owner/user and their management are accountable for the qualification and validation work outlined in this chapter.

Europe

European Commission Transatlantic Trade and Investment Partnership

In the pharmaceutical sector, it was noted that, in light of the progress achieved, the conclusion of a mutual recognition agreement of GMP

inspections by January 2017 was under consideration.

European Medicines Agency (EMA) Guideline on the Chemistry of Active Substances (EMA/454576/2016)

This guideline is effective from 15 May 2017 and replaces both "Note for Guidance on Chemistry of New Active Substances" (CPMP/QWP/130/96, Rev 1) and "Chemistry of Active Substances" (3AQ5a).

Its purpose is to set out the type of information required for the manufacture and control of active substances (existing or new chemical entities) used in a medicinal product. The differences in requirements for new or existing active substances are clarified in the relevant paragraphs of the guideline where applicable.

This guideline is not applicable to herbal, biological, biotechnological products, radiopharmaceuticals and radiolabelled products. Also, it does not apply to contents of submissions during the clinical research stages of drug development. Nevertheless, the development principles presented in this guideline are important to consider during the investigational stages.

This guideline is applicable to active substances that have been developed following a "traditional" or an "enhanced" approach, as described in ICH Q8-11.

As an acceptable alternative to submission of detailed active substance information in the application for marketing authorisation, the Active Substance Master File (ASMF) or the Certificate of Suitability (CEP) to the Monographs of the European Pharmacopoeia (Eur. Ph.) procedures may be used as described in Guideline on the Summary of Requirements for the Active Substance in the Quality Part of the Dossier, CHMP/QWP/297/97.

Tailored scientific advice to support step-by-step development of new biosimilars
The EMA will launch a pilot project



in February 2017 to test the added value and feasibility of tailored scientific advice for the development path of biosimilar medicines. Through this new initiative, the EMA aims to provide developers of biosimilars with advice on the studies/tests they should be conducting, on the basis of the quality, analytical and functional data they have already available for the medicine.

This is expected to better support the stepwise development of biosimilars that is recommended in EU guidelines. According to this approach, the extent and nature of the studies/tests required depend on the level and robustness of data already accumulated.

EMA Management Board: December 2016

The Board adopted the work programme and budget for 2017 and heard a Brexit update. Highlights reported were as follows.

- Update on Brexit preparations
- Work programme and budget for 2017
- Multinational assessment teams extended to post-authorisation procedures
- Revision of EMA's access to documents policy
- Updated framework for interaction with healthcare professionals.

European Directorate for the Quality of Medicines (EDQM) Enhanced sharing of information with Japanese regulatory authorities and strengthened collaboration with the Japanese Pharmacopoeia

EDQM agreed with Japan to improve the sharing of information related to therapeutic products that are common to both Europe and Japan, and to strengthen collaboration between the Eur. Ph. and Japanese Pharmacopoeia. The sharing of information will concern mainly the outcome of GMP inspections of manufacturing sites of

active pharmaceutical ingredients (APIs) of interest to both Europe and Japan. In addition, a 5-year Memorandum of Cooperation was signed which defines concrete measures for strengthening collaboration between the Eur. Ph. and Japanese Pharmacopoeia.

Eur. Ph. Commission adopts the monograph on sodium pertechnetate (99mTc) (accelerator-produced) injection (2891)

In 2009, the medical world faced a severe shortage of molybdenum-99 due to unexpected shutdown of some of the five nuclear research reactors that then supplied practically the whole world consumption of molybdenum-99.

As a consequence, most medical examinations using radio-pharmaceuticals could not be performed and were either omitted, or replaced by alternative diagnostic methods, if available. This event, together with the significant age of the nuclear reactors involved in the production of molybdenum-99 and the requirement to minimise radioactive waste, triggered the search for alternative production means for technetium-99m.

The Eur. Ph. has now adopted a monograph on sodium pertechnetate (99mTc) (accelerator-produced) injection (2891). Technetium-99m covered by this monograph is produced directly by proton irradiation of stable molybdenum-100. It is produced in accelerators, such as cyclotrons. There is an existing network of cyclotrons in nuclear medical departments that are capable in the emergency case to produce technetium-99m. This approach provides a viable alternative to the molybdenum-99 production in nuclear reactors and may compensate future shortages or provide a complementary production route for technetium-99m. The adoption of this European monograph should avoid future potential supply problems for the medical world and benefit patients.

(This looks to be a good example

of risk management/risk-based decision making – MH.)

Measures to reduce animal testing

A new non-mandatory Eur. Ph. General Chapter: Substitution of *in vivo* Methods by *in vitro* Methods for the Quality Control of Vaccines (5.2.14) aims at facilitating the transition from *in vivo* to *in vitro* methods by providing guidance on how to validate alternative *in vitro* methods in scenarios where a direct head-to-head comparison to an existing *in vivo* method is not possible.

Technical revisions of the general texts on Tests for Extrinsic Agents in Viral Vaccines for Human Use (2.6.16) and Cell Substrates for the Production of Vaccines for Human Use (5.2.3) were also adopted. The testing strategy as regards extraneous agents is to be established based on a risk assessment and the list of tests must be adapted depending on the extraneous agents that have the potential to contaminate the product. Molecular biology methods may be considered for the detection of specific viruses, while broad molecular methods may be considered for broad detection of viruses. In addition, the tests in suckling mice and control eggs are to be used only if a risk assessment indicates that the tests provide risk mitigation.

Guidance and roadmap for electronic submissions for CEP applications

This document provides guidance for electronic submissions for CEPs applications submitted to the EDQM. Information and requirements described in this document are intended to facilitate the handling and assessment of submissions for CEPs and to maintain their lifecycle even if the submission is not an electronic common technical document (eCTD).

This guidance should be applied for all electronic submissions sent to the EDQM in the context of applications for CEPs. From June



2016, the EDQM no longer accepts paper applications. All submissions should be in electronic format, irrespective of whether procedures are ongoing or not.

In addition, the EDQM roadmap for electronic submissions for CEP applications has been revised in order to align with the recently established Heads of Medicines Agencies (HMA) eSubmission Roadmap. For new CEP applications, eCTD format will become mandatory as of 1 January 2018. For revisions and renewal applications, eCTD format will become mandatory as of 1 January 2020. Transmissible spongiform encephalopathy-only submissions and submissions for substances for veterinary use only are exempt from this ruling.

Furthermore, applicants are reminded that as of 1 January 2017, submissions should be sent to the EDQM via the Common European Submission Portal.

API-Mix (or Mixtures) and CEPs

This document describes the approach to be taken regarding applications for CEPs for API-mix, which are mixtures of drug substances API with excipients, following the publication in April 2016 of Q&A on this subject by the Quality Working Party of the EMA.

These Q&A provide information on how to deal with API-mix, and to identify situations where it will be acceptable to use the ASMF/CEP procedures and perform manufacture under EU Guidelines to GMP Part II (except for the manufacturing steps such as sterilisation activities and the steps after sterilisation where EU Guidelines to GMP Part I is mandatory).

Eur. Ph. Commission concludes its pilot phase for monographs for bioterapeutics still under patent

The Eur. Ph. has worked with the innovators of these bioterapeutics (which are mainly single source) using an alternative monograph elaboration procedure (P4Bio pilot phase) to ensure that, when a patent

for one of these products runs out, a public standard for future products is already in place. During the elaboration process, the tests and procedures described in a monograph are subjected to extensive experimental testing by Eur. Ph. experts from Official Medicines Control Laboratories and by the EDQM Laboratory, and the draft monograph text is published for public consultation, thus ensuring the robustness of the standard.

Medicines and Healthcare Products Regulatory Agency (MHRA)

2015 GMP inspection deficiency data

The 2015 GMP inspection deficiency data trend has now been published and the GMDP (good manufacturing and distribution practices) Inspectorate has improved the way of gathering the deficiency data. The new data trending allows stakeholders to identify the following.

- The severity and frequency by the EU Guidelines to GMP references.
- The overall number of deficiencies by categories: Critical, Major, Other.
- The high impact versus high frequency issues.

The purpose of publishing the inspection deficiency data is to allow stakeholders to perform their own assessment against the deficiency findings as part of self-inspection and continuous improvement. Deficiency examples are included for each relevant chapter and annex for information.

(It is interesting that 'The Quality System' tops the list. Deficiencies noted for Annex 1 may also be of help to readers in understanding the need for and to comply with the soon to be issued revised Annex 1 – MH.)

Who inspects the inspectors (part 2)

Previously, the MHRA reported on the successful audit of their GMP

Inspectorate under the HMA Joint Audit Programme (JAP). Later that same month, the entire Inspectorate was assessed as part of the Benchmarking of European Medicines Agencies (BEMA) programme. The BEMA process is another HMA initiative but, unlike the JAP which is GMP specific, BEMA covers the whole of the Regulatory Agency. The programme has the broad aim to contribute to the development of a world-class medicines regulatory system based on a network of agencies operating to best practice standards. It is based on assessment of the systems and processes in individual agencies against a set of indicators which have been agreed in the following areas.

- Management systems.
- Assessment of marketing authorisation applications.
- Pharmacovigilance (drug safety) activities.
- Inspection services.

Annex 16 Certification by a Qualified Person and Batch Release – FAQ – part 1

This blog posting contains the first in a series of frequently asked questions (FAQs) related to the updated EU Guidelines to GMP Annex 16. The Q&As cover sampling and testing (6 questions) and integrity of imports (2 questions).

(This is a very useful blog posting. It is an area where the MHRA are probably seeing "issues" during inspections. Sites/qualified persons would be well advised to review their practices against it as soon as possible and use it to prepare for their next inspection. Look out for part 2 of the Q&A – MH.)

API supply chains blog – part 2

The second part of this blog focuses on the finished drug product manufacturer utilising the API. Specifically it covers supply chain traceability, registration of suppliers, audits of API suppliers, confirmation at inspection, and qualified person



responsibilities.

Medregs blog

This blog will feature posts from experts who work right across the regulatory process. They will share their insights and experiences on a range of topics to help you stay informed, engage with MHRA processes more effectively, and find out more about what the MHRA does do to protect public health. Current postings within the blog are on the topics of developing the strategy for pharmacopoeial quality standards for biological medicines, and batch-specific variations.

GMP Inspectorate compliance management escalation processes

The MHRA has published information in its blog to give an overview of its GMP escalation processes. Since the two escalation processes were introduced, a wide variety of cases have been referred across different licence types, dosage forms, licence activities, and have included the following.

- Laboratories and manufacturers.
- Finished product and API manufacturing sites.
- Overseas and UK sites.
- Licensed and unlicensed products.
- Medicines and blood products/components.

A total of 26 new escalation cases were started in 2016.

Exports and customs procedures

This blog post suggests ways in which you can actively prevent your company receiving deficiencies in the area of lack of documentation and poor control, or lack of visibility within the supply chain, simply by making small changes to and increasing your understanding of export procedures and requirements.

Both the good distribution practice (GDP) and GMP inspectorate will be routinely requesting full export

documentation at inspection – and this extends to the Customs Handling of Import and Export Freight entry – bills of landing or airway bills, export licences where applicable, and any certificates of origin that may be required for that particular commodity to be sent to the destination country.

Reducing errors in licence applications

The MHRA's Process Licensing Team typically receives about 840 manufacturing authorisation-related applications per year. Unfortunately, around 30% of all applications result in Requests for Further Information (RFI) before they can be accepted for processing. They, therefore, require follow-up before the detailed assessment work can get under way!

The purpose of this blog post is to help reduce the number of applications requiring RFIs, by raising awareness of the common mistakes. RFIs will delay the application process and can be costly in terms of time and effort to resolve. They cause frustration for applicants as well as MHRA staff, but in most cases they are avoidable!

2016 MHRA GMP Symposium

The MHRA has published a summary record of this event.

Control of API supply chain

The supply chain for APIs has been increasing in complexity for a number of years with the potential for a number of players to be involved, with multiple possible routes around the world available. Where complex supply chains are in place, along with a limited understanding of the overall picture, the risk of falsified APIs entering the supply chain unnoticed is significantly increased.

A number of controls have been implemented within Europe to minimise the risk of falsification and the two blog posts in this series highlight a number of these and provides background on what is required of the various parties

involved. This first blog post concentrates on the players in the API supply chain.

MHRA Laboratories Symposium Q&A

The symposium provided an opportunity for the laboratory inspectors to interact and share expectations with stakeholders on current regulatory challenges, as well as hearing participant's feedback and questions. Inspectors presented on hot topics such as the GxP Data Integrity Guidance and Organisation for Economic Co-operation and Development (OECD) Guidance Document No. 17 Application of the GLP [good laboratory practice] Principles to Computerised Systems. With so many delegates present and the opportunity for delegates to submit questions electronically, it was not possible to answer all questions submitted at the symposium itself, however, the MHRA have sorted through some important questions which they didn't have time to answer and have posted them on the MHRA blog.

New Orange and Green Guides 2017

The MHRA has launched its latest guide of UK pharmaceutical regulations, EU directives and guidance. The Orange and Green Guides are aimed at manufacturers and distributors of human medicines. They have been revised and updated to keep industry informed of the latest regulations.

The Orange Guide has been updated to incorporate changes and additions made to the detailed EU Guidelines to GMP and the revised EU Guidelines to GDP. There are new sections on the following.

- GMP for excipients.
- Guidance on revised Annex 16 of the Guidelines to GMP.
- Data integrity definitions and guidance for industry.

The new 2017 edition of the Green Guide provides a single



source of guidance to, and legislation for, the distribution of medicines in Europe and the UK. There are new sections on the following.

- The guidelines on principles of GDP of active substances for medicinal products for human use (2015/C 95/01).
- Matters relating to unlicensed medicines.
- Sourcing and exporting medicinal products – non-European Economic Area (EEA) countries.
- Data integrity.
- The EU regulation on safety features for medicines.

International

ICH

ICH Q11 Q&As

In order to facilitate the implementation of the Q11 Guideline, the ICH Q11 IWG has developed a series of Q&As.

Since the ICH Q11 guideline was finalised, worldwide experience with implementation of the recommendations on the development and manufacture of drug substances has given rise to requests for clarification relating to the selection and justification of starting materials.

This Q&A document is intended to provide additional clarification and to promote convergence on the considerations for the selection and justification of starting materials and on the information that should be provided in marketing authorisation applications and/or master files. The focus of the Q&A document is on chemical entity drug substances. The scope of this Q&A document follows that of ICH Q11.

ICH Q11 is applicable to drug substances as defined in the Scope sections of ICH guidelines Q6A and Q6B, but might also be appropriate for other types of products following consultation with the appropriate regulatory authorities. ICH Q11 does not apply to contents of submissions during the clinical

research stages of drug development. Nevertheless, the development principles presented in ICH Q11 and this supporting Q&A document are important to consider during the investigational stages. Generally, it is anticipated that API starting materials that have already been accepted by regulatory authorities (e.g. for use in authorised medicinal products) would not need to be re-justified against the ICH Q11 general principles or the recommendations included in this Q&A document, unless significant changes are made to the manufacturing processes and controls. However, a starting material accepted for one manufacturer's process may not be considered acceptable for a different manufacturer's process, if the proposal does not comply with the guidance in ICH Q11.

Designation of starting materials should be based on process knowledge for the intended commercial process. It is emphasised that all of the general principles in ICH Q11 Section 5 should always be considered holistically, together with the clarifications in this Q&A document, rather than applying a single general principle or Q&A clarification in isolation.

Pharmaceutical Inspection Co-operation Scheme (PIC/S) Strong stance on European Commission's proposed stand-alone Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products

On 24 February 2017, PIC/S sent a letter to the European Commission on this topic, regretting the complete absence of cooperation and drawing attention to the Commission's responsibilities resulting from the development of its proposed stand-alone advanced therapy medicinal products (ATMP) GMP guidelines, which PIC/S states will not only lower GMP standards for ATMP at the risk of patients but also lead to an internationally non-harmonised approach to the

implementation of GMP for ATMP. Amongst other things, the PIC/S letter states the following.

- The PIC/S Committee is unanimously concerned about the impact on public health and for the safety of patients that the ATMP GMP Guideline will cause.
- Due to the European Commission's initiative in the field of ATMP, the PIC/S GMP Guide and the EU GMP Guide will no longer be equivalent.
- The decision to amend Annex 2 and repeal Annex 13 of the EU GMP Guide is a serious setback in terms of co-operation between the EU and PIC/S.

Letter of agreement with the EEA HMA

PIC/S has a signed letter of agreement with the HMA, which entered into force on 15 August 2016, by which PIC/S and the HMA agree to cooperate in exchanging information in the context of the EEA JAP of GMP Inspectorates and the PIC/S Joint Reassessment Programme of Participating Authorities. (HMA is the Heads of the National Competent Authorities whose organisations are responsible for the regulation of medicinal products for human and veterinary use in the EEA.)

Revision of PIC/S GMP Guide (PE 009-13)

Four Chapters of the PIC/S GMP Guide have been revised.

- Chapter 1 on "Quality Management" (which has become "Pharmaceutical Quality Systems").
- Chapter 2 on "Personnel".
- Chapter 6 on "Quality Control".
- Chapter 7 on "Contract Manufacture and Analysis" (which has become "Outsourced Activities").

The revised Chapters are based on the equivalent Chapters of the EU Guidelines to GMP with some minor differences in terms of language.



Chapters 1, 2 and 7 have been aligned to ICH Q10 and the principles of "Pharmaceutical Quality System" have been integrated. A section on consultants has been added in Chapter 2. The scope of Chapter 7 has been expanded beyond the scope of "contract manufacture and analysis". Both Chapters 1 and 7 have been renamed to reflect the changes. In Chapter 6, all sections have been reviewed and amended and a new section on "Technical transfer of testing methods" has been added.

Products

Sterility concerns - cephalosporin APIs made by Antibioticos Do Brasil LTDA

Following an inspection, the Italian Competent Authority has published a non-conformance report in the EUDRAGMP database. It bans the import of certain APIs and recommends that the EDQM should consider the withdrawal of the CEP for R0-CEP 2010-026-Rev 01 – Ceftazidime pentahydrate with sodium carbonate for injection sterile. Similar concerns had been expressed in an earlier US FDA report.

Tri-Coast Pharmacy Inc. voluntarily recall all sterile products prepared 17 May 2016-17 November 2016

Tri-Coast Pharmacy Inc. (Juno Beach, FL, USA) is voluntarily recalling all sterile products prepared between 17 May 2016 and 17 November 2016 and that remain within expiry due to the FDA's concerns over the lack of sterility assurance of the drugs

named in this recall.

Administration of a drug product intended to be sterile that has microbial contamination has the potential to result in serious infections which may be life-threatening. No portion of any lot of these medications has been found to be non-sterile, but the FDA is concerned that the conditions under which they were produced introduce a lack of sterility assurance for these products. To date, Tri-Coast Pharmacy has received no adverse event reports for these products.

Documents

Active Pharmaceutical Ingredients Committee (APIC) Guidance on Aspects of Cleaning Validation In Active Pharmaceutical Ingredient Plants

The 2016 revision of this guidance document has now been made to bring it in line with the EMA Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities. The document reflects the outcome of discussions between APIC member companies on how cleaning validation requirements could be fulfilled and implemented as part of routine operations. In addition, APIC has aligned this guidance with the International Society for Pharmaceutical Engineering Risk Manufacture of Pharmaceutical Products Guide that follows the quality risk management (QRM) processes as described in the ICH

Q9 Guidance on Quality Risk Management.

The subject of cleaning validation in API manufacturing plants has continued to receive a large amount of attention from regulators, companies and API customers. The integration of cleaning validation within an effective quality system supported by QRM processes should give assurance that API manufacturing operations are performed in such a way that risks to patients related to cleaning validation are understood, assessed for impact and are mitigated as necessary.

The main changes were introduced in Chapter 4 Acceptance Criteria. Six specific areas are addressed.

- Acceptance criteria.
- Levels of cleaning.
- Control of the cleaning process.
- Bracketing and worst case rating.
- Determination of the amount of residue.
- Cleaning validation protocol.

Also, FAQ are answered to give further guidance on specific points related to cleaning validation.

For further information on these and other topics, we suggest you refer to the websites of relevant regulatory bodies and to current and past editions of "GMP Review News" published by Euromed Communications. To subscribe to this monthly news service contact





PHARMA IN PLENARY

Improving access to medicines

by Dr Nicola Davies

Ensuring better market access is essential for all stakeholders in the pharmaceutical industry. For patients, it is how they attain improved health outcomes, which is the ultimate goal of all companies in the industry. For healthcare professionals, it helps them facilitate better health services. For governments, it results in lower healthcare costs and assists in creating a more economically productive population. For businesses, it is the main factor for commercial success¹.

It is, therefore, unsurprising that market access is a key theme for the European Parliament, specifically in relation to three recent notable events: **1)** the resolution on recommendations for options to improve access to medicines; **2)** response to the European Union's (EU's) position on the United Nations (UN) High-Level Panel (HLP) on Access to Medicines at the World Intellectual Property Organisation (WIPO); and, **3)** a call to guarantee the right of universal access to medicines in the Transatlantic Trade and Investment Partnership (TTIP) negotiations.

Recommendations: options for improving access to medicines

Due to reported issues in access to medicines across the globe, the Parliament released a resolution early in March that calls for "national and EU-wide measures to guarantee the right of patients to universal, affordable, effective, safe, and timely access to essential and innovative therapies, to guarantee the sustainability of EU public healthcare systems, and to ensure future

investment in pharmaceutical innovation"².

Some of the specific recommendations call on Member States to develop shared health technology assessment processes and shared criteria for pricing and reimbursement decisions at the national level. Member States are also urged to secure accessibility and density of pharmacies in urban and rural areas, equipping these with appropriate business hours, staff members and counselling services.

The reinforcement of generics and biosimilar use is also stressed. The Parliament calls on the European Commission to amend the Transparency Directive to guarantee timely entry of generics and biosimilars in the market. In addition, the Commission is called on to ensure that the orphan drug regulatory framework and the timely approval of rare disease treatments are effectively implemented. Reports of cancer medicine shortages in Romania have also elicited a recommendation on the Commission and Council to enable an annual reporting of medicine shortage^{2,3}.

In general, the Parliament recommends that the Commission and Council employ various access-promoting measures, such as early dialogue between stakeholders, innovative pricing models, voluntary joint procurements, and voluntary cooperation in price negotiations. Part of these measures must extend towards improving EU support of global initiatives for access in developing countries. With approximately 2 billion people still unable to receive essential medicines, Big Pharma have taken strides that align with this initiative. Johnson & Johnson, for instance, created its Global Public Health strategy early last year to aid in solving pressing public health needs.

The initiative entails delivering holistic solutions to urgent issues by empowering and working closely with local healthcare professionals, researchers and businesses⁴. Both Takeda and GlaxoSmithKline (GSK) have also adopted an innovative pricing scheme for specific developing markets where prices are lowered at a level that matches with the market's ability to pay^{5,6}.

The EU's position on the UN High-Level Panel on Access to Medicines at WIPO

Despite the solid intellectual property (IP) system in Europe, a UN Secretary-General's HLP on Access to Medicines report stated that there is "policy incoherence between the justifiable rights of inventors, international human rights law, trade and public health,"⁷ suggesting tension between the IP rights of inventors and the right to health⁸.

The EU's stand at the WIPO was in defense of the IP global framework, underscoring that it encourages product innovation. The mission of WIPO remains to be the development of an effective and balanced international IP system that benefits all stakeholders involved. Thomas Bombelles, Head of Global Health at the WIPO Global Issues Sector, however, admits that sustaining both innovation and medicine access continues to be a challenge⁸.

Regardless, in a written contribution to the Panel, the European Commission indicated that it did not share in the official EU position regarding the HLP's assumption. The European Parliament Working Group on Access to Medicines and Poverty-Related Diseases expresses strong support for the HLP recommendations and



calls on the EU to acknowledge the benefit of implementing these to help ensure “both innovation and affordable and suitable access to the needed innovative medical tools in Europe and beyond”⁷.

Balancing IP rights incentives with right to health is an effort that pharma companies can individually practice amidst the current international IP framework. GSK, for instance, has the highest number of research projects focused on high-priority product gaps. For research in HIV, tuberculosis, malaria and neglected tropical diseases, the company shares IP with many local partners⁹.

Guaranteeing the right of universal access to medicines in the TTIP negotiations

Regarding questions on the potential impact of negotiations in the TTIP on public health sector and access to medicines, the Commission clarifies that the EU's IP rights and pricing/reimbursement regulations on pharmaceuticals are not part of the TTIP objectives¹⁰.

The EU trade agreements exclude publicly funded health services in areas such as education, water, health and social services, as indicated in the 2015 Joint Statement on Public Services of Commissioner Cecilia Malmström and Ambassador Michael Froman¹¹. Therefore, governments involved in the TTIP are not precluded from adopting regulations that help ensure quality of services and are not required to privatise services or expand their existing range of public services in these four areas. This approach will be followed in the TTIP.

According to a response provided on behalf of the Commission, the EU has “a solid and comprehensive intellectual property rights system,” which supports innovation and global competition. In addition, the Member States possess “some of the most efficient and inclusive public health systems in the world”. The Commission states there is no cause for concern in the TTIP clauses regarding access, pricing and reimbursement of medicines. Hence, no new regulations on drug pricing need to be entertained¹⁰. In addition, pharma companies aiming to enter the local markets of Member States must, therefore, adhere to the local marketplace regulations.

Pharma companies must stay abreast with regulations that may impact on the global pricing and reimbursement landscape and ensure that policies are adhered to in the spirit of ensuring access to innovative medicines.

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www.industrialpharmacy.eu



bottled brown

Making a medicine: science, technology and odyssey

Morphine, my chosen medicine, starts its journey on the farm. Morphine is potent and has caused wars.

Opium contains morphine and opium poppy extract relieves pain. Humankind has used *Papaver somniferum* for at least 3500 years. It biosynthesises many alkaloids, one being morphine ($C_{17}H_{19}NO_3$).

Today, generally, machines harvest the whole plant. "Poppy straw" leaves the farm.

Factories

The first factory manufactures the active pharmaceutical ingredient (API) using a traditional biotechnology. Various initial processes, such as solvent extraction and pH adjustment, purify the plant material; different alkaloids precipitate within specific ranges. Adding dilute sulfuric acid synthesises the sulfate. Pharmaceutical scientists oversee and outside pharmaceutical experts audit.

From the second factory, pharmaceutical company staff procure that morphine sulfate. They anticipate what the API will become. That is a leap of faith: a prophesy. Delivery occurs.

Machines labour. Enrobed experts attend, speaking their own jargon, inhabiting their own world. They follow their own customs and conventions. They walk between familiar landmarks and, between the machines, feel at home.

Excipients such as lactose are added. The production line

continues: granulation, tableting, blister packing, addition of patient information leaflets, box labelling and sealing. An original design and a system of good manufacturing practice encourages adequate quality. This includes premises, equipment, documentation, production, quality control, self-inspection, handling of complaints and product recall. Within the European Union, only a qualified person can certify approval of release to market of a batch. That is its "birth certificate" and, on signing, batch value leaps.

Watchers

Manufacturing is a sort of panopticon ("all-seeing"). The political scientist Jeremy Bentham so named a building around 1791. People are controlled. Experts, including pharmacists, judge the batch. They are themselves judged. That ensures they possess sufficient knowledge. They have passed examinations when their performance was ranked with other examinees: they only passed if their performance was good enough. Continuing performance and behaviour is also examined and controlled. Their professional body and courts may discipline individuals performing under the norm.

The industrial pharmaceutical machine watches everyone. That includes the controllers. Watchers are watched. Manufacturers may resent heavy regulation but that ratchets up prestige and power.

Industrial pharmacy spawns more records about the batch, such as audits, batch records, registers and samples. They slumber in stores after most of the medicine has

physically disappeared. Records wait in case problems occur when records would carry clout.

Staff know they have made the batch well. They know they have tested it well. It has been scrutinised and found good. Staff feel proud.

Patients

Agonised patients swallow the medicine and their guts absorb the API. The patient's bodies assimilate the API. The morphine molecule and analgesic receptor site on cells have certain features including size, shape and stereoscopic structure. Features fit together, reducing electrical, nervous impulses. Pain deadens.

The patients' bodies chemically degrade the morphine. Most conjugates with glucuronic acid in the liver and gut. Morphine's major metabolite is morphine-3-glucuronide. The patients' urine enters the sewer.

The morphine degradate and other liquid and solid waste flow through the sewerage system. Waste is sprayed upon an inert medium. Gas updrafts, and a range of bacteria, further split the degradate. Released energy warms the filter, speeding bacterial growth. *Pseudomonas putida M10* exclusively uses morphine as a carbon and energy source. Protozoa, worms and moth fly larvae and, in turn, birds, especially starlings, graze the bacterial film. Bird droppings contain carbon and nitrogen. They fertilise soil.

Opium poppies grow in soil. Around and around the cycle goes.

Malcolm E Brown



January Bureau meeting

A meeting of the Bureau was held at the offices of the Associazione Farmaceutici dell'Industria in Milan, Italy. The main items on the agenda were the General Assembly (GA) and the Workplan until May 2017. Two Working Groups were chosen for the GA:

"Quality Systems in Serialisation" led by EIPG Vice-President Maurizio Battistini (Association Française des Professionnels des Titres, Switzerland) and facilitated by a speaker from Aesica

"Value Based Outcomes in the Pharmaceutical Industry" led by EIPG Past-President Gino Martini Royal Pharmaceutical Society (RPS), UK and facilitated by Barbara Freischem (European Biopharmaceutical Enterprises, EFPIA).

Technical documents

EIPG is an eligible organisation to have direct involvement in the activities of the European Medicines Agency. The following technical documents are out for consultation and have deadlines for comment during May.

- Reflection paper providing an overview of the current regulatory testing requirements for medicinal products for human use and opportunities for implementation of the 3 Rs.
- Consultation on the revised Volume 2C guidelines on excipients in the labelling and package leaflet of medicinal products for human use.
- Concept paper on the need for revision of note for guidance on quality of water for pharmaceutical use (human and veterinary).

Any reader who wishes to comment on any of the above should contact their national delegate and Piero Iamartino, EIPG Vice-President (pieroiamartino@gmail.com)

Shortages of medicines

In January, the European associations representing manufacturers of medicinal products, distributors, wholesalers and the European professional associations representing pharmacists, including EIPG, announced a series of

recommendations on the provision of information designed to tackle shortages. The full report is published in this issue (pages 7–16) and is also available on the EIPG website under "Position Papers".

During the EAHP (European Association of Hospital Pharmacists) Congress, Jane Nicholson presented her COST Working Group's preliminary findings on the causes of shortages of medicines. She also attended a formal meeting organised by EAHP with a number of associations representing European pharmacists from the various areas of pharmacy. The major activities of each association were discussed.

EIPG webinars for members

In February, a further webinar was held in conjunction with our Irish association PIER (Pharmacists working in Industry, Education and Regulation) and the University College Cork. The subject was the Falsified Medicines Directive and speakers were Anne Hayes, Inspection Manager in the Compliance Department at the Health Products Regulatory Authority in Ireland and Claude Farrugia, President of EIPG. It attracted 172 members to register for the event.

Anyone with ideas for future webinar subjects and speakers should please advise Jane Nicholson (jane@nicholj.plus.com).

EPSA

Maurizio Battistini (EIPG Vice-President European Affairs) and Thomas Lion and Frank Peeters (Belgian Professional Association of Pharmacists working in the Life Science Industry (UPIP-VAPI), Belgium) attended the EPSA (European Pharmaceutical Students' Association) annual reception held at the European parliament. The following is a summary of their report.

Following a presentation of EPSA's current activities, the main topic of the day was "Self-Care: Empowering Pharmacists for Enhanced Access, Quality and Safety". A debate was organised with a group of experts.

- Lieve Wierinck: Member of the European Parliament.

- Rajesh Patel: President of PGEU (Pharmaceutical Group of the European Union).
- Aneela Ahmed: President of European Patients Forum Youth Group.
- Maud Perrudin: Legal and Regulatory Affairs Manager, Association of the European Self-Medication Industry.
- Aurélien Perez: Team Leader; Cross-Border Healthcare & Health Unit, DG Santé, European commission.

The audience included about 100 pharmacy students and this hot topic was discussed in a dynamic atmosphere. The following are some key reflections of the meeting.

- Patients must be more involved in the treatment of chronic disorders.
- Self-care is not self-diagnosis.
- Due to modern technology, patients have accessed more information before interacting with healthcare professionals. This is a challenge for future pharmacists.
- Improving control of drugs from the internet is key to secure self-medication.
- Drugs outside pharmacy are dangerous.
- Pharmacists must develop and better use their role as drug experts.
- Visibility of non-prescription drugs must be improved in the retail environment.
- A pharmacist is a key player to support the patient regarding treatment adherence especially for young people.

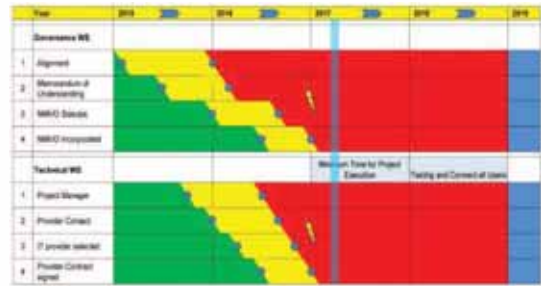
In conclusion, self-care will take more importance in the future drug market and pharmacists will be a key player to ensure patient safety and well-being in this evolution.

EPSA and EIPG launched their 2017 programme of joint webinars with a session on the Falsified Medicines Directive. The speakers were Sue Kilby (RPS, Great Britain) and EIPG President Claude Farrugia.

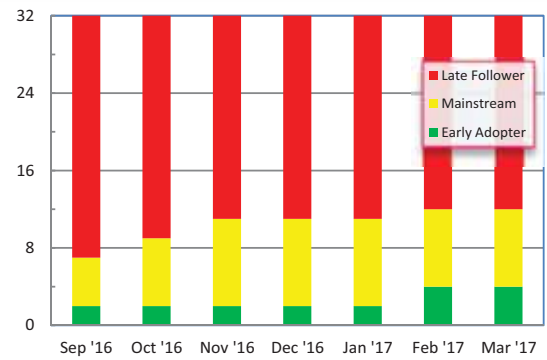
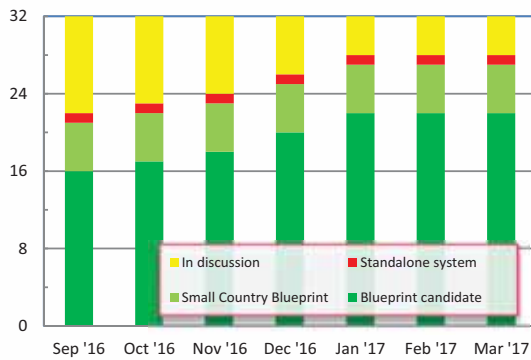
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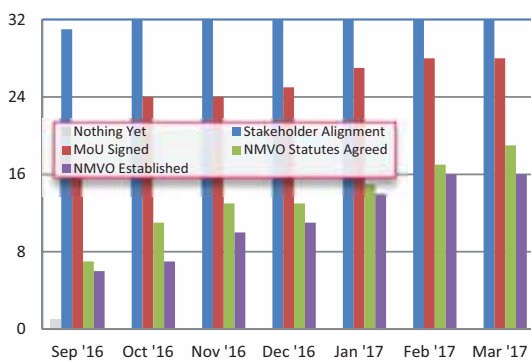
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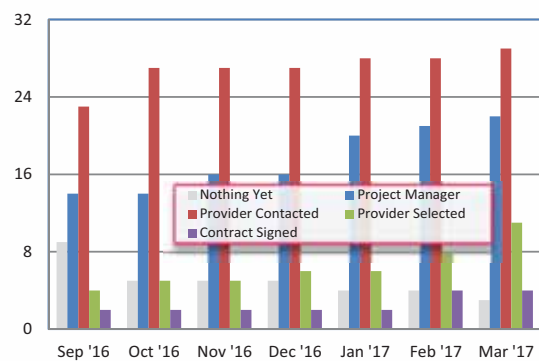
Blueprint Tendency



Governance Workstream



Technical Workstream



events

MAY 2017

1–4 May 2017 – Athens, Greece
4th Annual International Conference on Pharmaceutical Sciences

www.atiner.gr/pharmako

3–4 May 2017 – Philadelphia, PA, USA

World Drug Safety Americas 2017
www.healthnetworkcommunication.com

12–13 May 2017 – London, UK
The Clinical Pharmacy Congress – The Home of Clinical Pharmacy
www.pharmacycongress.co.uk

15–17 May 2017 – Munich, Germany
7th European Biosimilars Congress
<http://biosimilars-biologics.pharmaceuticalconferences.com/europe/>

17–19 May 2017 – London, UK
World Precision Medicine Congress 2017
www.terrapinn.com

21–24 May 2017 – Stockholm, Sweden
6th Pharmaceutical Sciences World Congress
<http://pswc2017.fip.org/>

22–23 May 2017 – Chicago, IL, USA
6th World Pharmacists & Clinical Pharmacy Annual Congress
<http://annualmeeting.conferenceseries.com/pharmacists/>

23–24 May 2017 – San Diego, CA, USA
World Biosimilar Congress USA 2017
www.terrapinn.com

29–31 May 2017 – Osaka, Japan
International Conference and Exhibition on Nanomedicine and Drug Delivery
<http://nanomedicine.pharmaceuticalconferences.com/>

JUNE 2017

5–7 June 2017 – Arlington, VA, USA
2017 ISPE/FDA Quality Manufacturing Conference
www.ispe.org

12–13 June 2017 – Taipei, Taiwan
International Conference on Pharmaceutical and Biomedical Engineering
<http://engineering.pharmaceuticalconferences.com/>

13–14 June 2017 – Berlin, Germany
2nd Europe PDA Annual Meeting
www.pda.org

19–20 June 2017 – Philadelphia, PA, USA
3rd International Conference on Biopharmaceutics and Biologic Drugs
<http://biopharmaceutics.pharmaceuticalconferences.com/>

27–28 June 2017 – Valencia, Spain
Advanced Therapy Medicinal Products
www.pda.org

JULY 2017

3–5 July 2017 – Bangkok, Thailand
4th Annual Congress on Drug Discovery & Designing
<http://drugdiscovery.pharmaceuticalconferences.com>

10–11 July 2017 – Jakarta, Indonesia
8th Global Pharmacovigilance & Drug Safety Summit
<http://globalpharmacovigilance.pharmaceuticalconferences.com/>

10–12 July 2017 – Madrid, Spain
9th Annual European Pharma Congress
<http://europe.pharmaceuticalconferences.com/>

17–19 July 2017 – Munich, Germany
9th International Conference and Exhibition on Pharmacovigilance & Drug Safety
<http://pharmacovigilance.pharmaceuticalconferences.com/>

24–25 July 2017 – Rome, Italy
13th International Conference and Exhibition on Pharmaceutical Nanotechnology
<http://nanotechnology.pharmaceuticalconferences.com/>

31 July–1 August 2017 – Milan, Italy
3rd World Congress and Exhibition on Antibiotics and Antibiotic Resistance
<http://antibiotics.pharmaceuticalconferences.com/>

AUGUST 2017

17–18 August 2017 – Los Angeles, CA, USA
8th Annual Global Pharma Summit
<http://www.clocate.com/conference/8th-Annual-Global-Pharma-Summit-2017/62641/>

24–25 August 2017 – Birmingham, UK
2nd International Conference and Expo on Generic Drug Market and Contract Manufacturing
<http://generic-market.pharmaceuticalconferences.com/>

31 August–1 September 2017 – Brussels, Belgium
19th Nano Congress for Next Generation
<http://nanocongress.conferenceseries.com/>

SEPTEMBER 2017

1–2 September 2017 – Las Vegas, NV, USA
5th International Pharmacy Conference
<http://pharmacy.pharmaceuticalconferences.com/>

5–7 September 2017 – Hatfield, UK
8th International PharmSci Conference 2017
www.apsgb.co.uk

7–9 September 2017 – Paris, France
6th World Congress on Biopolymers
<http://biopolymers.conferenceseries.com/>

10–14 September 2017 – Seoul, Republic of Korea
77th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2017
<http://www.fip.org/seoul2017/>

11–13 September 2017 – Washington, DC, USA
PDA/FDA Joint Regulatory Conference
www.pda.org

20–21 September 2017 – Dublin, Ireland
3rd International Conference on Advanced Clinical Research and Clinical Trials
<http://clinicalresearch.pharmaceuticalconferences.com/>

