HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Medicinal Product Shortages

Two-Year Review

November 2022

CONTENTS

GLOSSARY OF TERMS

Healthcare professionals	Healthcare professionals are stakeholders that include prescribers, pharmacists and nurses.
Impact assessment	An impact assessment is performed to determine the impact of a potential or actual shortage on patients.
Manufacturer	The manufacturer is a stakeholder that has been authorised to produce medicinal products. The manufacturer may or may not also be the marketing authorisation holder (MAH).
Marketing authorisation holder (MAH)	The MAH is the stakeholder whose name the marketing authorisation for a medicinal product has been granted. The MAH is responsible for all aspects of the medicinal product, including quality and compliance with the conditions of the marketing authorisation.
Marketing authorisation number	Each authorised medicinal product has a specific reference number on the packaging. The marketing authorisation number usually takes the form of a sequence of letters followed by numbers. For example, the letters can be PA, PPA, DPR or EU.
Medicinal product shortage	A medicinal product shortage occurs when the supply of a medicinal product is inadequate to meet the needs of patients.
Notification	A notification is a communication of a shortage from a stakeholder.
Wholesale distributor	The wholesale distributor is a stakeholder authorised to distribute medicinal products.

1 EXECUTIVE SUMMARY

Since 2018, the Health Products Regulatory Authority (HPRA) has been working with stakeholders to develop and implement a multi-stakeholder approach to tackling medicine shortages. Building on the agreed principles and definitions of the Medicine Shortages Framework ('the framework'), this review is the first time data on shortages in Ireland has been collected in such a comprehensive and quantifiable manner. The insights gained will provide vital information to guide future strategies to optimise handling shortages and their prevention.

This review was performed using the data gathered by the HPRA under the framework during 2019 and 2020. The information includes product details, impact status, start and end date, proposed mitigation/prevention response and causes. The framework went live in September 2018, but this was, in effect, a live 'use and learn' period, as stakeholders were getting familiar with using the framework. Consequently, the analysis did not include information from this first phase in 2018, focusing on the entire calendar years 2019 and 2020.

There have been 1493 reports of potential shortages to the HPRA in the last two years, and these have come from a wide range of stakeholders involved in supply to patients and patients themselves or their representatives. Up to April 2020, 94% of shortages reported to the HPRA have been resolved. The holistic approach involving a coordinated approach from multiple stakeholders has enabled a comprehensive framework to tackle availability issues nationally.

Although the review data indicates significant improvements have been made in addressing medicines shortages, it also highlights the remaining challenges. This includes the timing of a shortage notification to the HPRA, which is, on average, less than two weeks before a shortage occurs. The notification of possible shortages to the HPRA is the basis for triggering the framework and the associated coordinated multi-stakeholder response as required, including preventative or mitigation strategies. The proximity of the notification timing to the actual shortage occurrence reduces the ability to identify and implement actions to prevent the shortage from occurring.

However, the data from the review has also presented opportunities. Generally, the medicine shortages framework focuses on finding solutions once a potential shortage is identified or a medicine becomes unavailable. The last two years of experience illustrate that early communication and collective approaches effectively prevent shortages or limit their impact on patients if this is not possible. This was demonstrated most recently in the context of the COVID-19 pandemic, particularly during the first wave, which resulted in a significant unexpected demand for specific medicines. The close communication and aligned strategies among key stakeholders such as the Department of Health, the Health Service Executive, the HPRA, healthcare professionals and the pharmaceutical industry as a whole ensured an effective response to the challenges created by the pandemic and the need for continuity of treatment for patients.

The data collected as part of the review presents quantifiable support and evidence to inform and underpin the next steps in developing the framework. This includes measures to optimise the existing framework and actions to create and implement preventative and mitigation strategies to address the causal and exacerbating factors that drive shortages as identified via the experience to date.

Key recommendations from the review are based on the twin strategies of optimising the framework and shortage prevention/mitigation. The recommendations are outlined below. Each recommendation has associated proposed implementation actions that are summarised below in Table 1.

- **Optimisation of the framework.**
  - Actors in the supply chain, such as MAHs, manufacturers and wholesalers, should notify the HPRA of a potential or actual shortage as soon as possible in advance of any shortage (Recommendation 1).
  - Increase transparency relating to shortage information (Recommendation 2).
  - MAHs should increase the accuracy of notification detail provided to the HPRA (Recommendation 3).

- **Prevention and mitigation strategies.**
  - Optimise pharmaceutical quality systems to strengthen the reliability and resilience of supply chains throughout the lifecycle of a medicine (Recommendation 4).
  - Increase resilience in the supply chain, considering known vulnerabilities (Recommendation 5).
  - Improve communication between stakeholders (Recommendation 6).
  - Promote fair and equitable distribution to meet the needs of patients (Recommendation 7).
  - Take appropriate steps to minimise the risk of parallel trade exacerbating shortages (Recommendation 8).

Table 1: Recommendations and associated implementing actions

	Recommendation	Implementing action
1	Actors in the supply chain, such as MAHs, manufacturers and wholesalers, should notify the HPRA of a potential or actual shortage as soon as possible in advance of any shortage.	
		1.1: The HPRA will engage with stakeholders to understand barriers to earlier notifications to encourage timely notifications. This will include the potential for developing alternative notification mechanisms (e.g. an Excel file). The current notification template will be updated to explicitly advise that the initial notification of a potential shortage can be the minimum details, with additional information to be provided as a follow-up.
2	Increase transparency relating to shortage information.	
		2.1: The HPRA will publish confirmed low-impact shortages.
		2.2: The HPRA will develop case studies to improve stakeholders' understanding of the role of the HPRA in the coordination of management of shortages and the approach that is taken to prevent potential shortages or mitigate their impact.
		2.3: The HPRA will promote the development of international cooperation, thereby increasing information sharing and transparency, which will optimise the national shortages framework.
3	MAHs should increase the accuracy of notification detail provided to the HPRA.	
		3.1: The HPRA will engage with stakeholders directly to further develop the notification process, host training sessions for industry notifiers, and develop practical guidance for completing the notification form based on the engagement outcomes.
4	Optimise pharmaceutical quality systems to strengthen the reliability and resilience of supply chains throughout the lifecycle of a medicine.	
		4.1: Industry stakeholders should support continual optimisation of the pharmaceutical quality system to strengthen the reliability and resilience of the medicine supply chain, thereby enabling better prevention of shortages.
		4.2: The HPRA will continue to engage with the medicine regulatory network to promote mechanisms whereby optimisation of the regulatory processes can contribute to enabling better reliability and resilience of supply chains, thereby enabling better prevention of shortages.
5	Increase resilience in the supply chain, taking into account known vulnerabilities	
		5.1: Companies should ensure that they consider the potential for fluctuations in the supply chain, particularly for medicines with limited clinical alternatives, given the potential for high impact shortages.

		5.2: MAHs and manufacturers should ensure enough buffer stock to allow for unexpected delays during manufacturing site changes or ownership transfers.
6	Improve communication between stakeholders	
		6.1: Each stakeholder should continue to establish effective and frequent communication between the different actors such as within the different teams or affiliates of the MAH as well as between the MAH, the relevant manufacturing sites and the wholesaler.
		6.2: Stakeholders involved in developing clinical treatment or public health measures should consider the impact of such changes on demand for some medicines. Where there is a potential for a significantly increased demand for individual medicines, arrangements should be made to communicate this to suppliers to enable them to adjust supply accordingly.
7	Promote fair and equitable distribution to meet the needs of patients	
		7.1 Stakeholders should not order or dispense more stock than normal where there is a potential or actual shortage. This has the effect of creating a supply issue where there may not have been one. Additionally, in a shortage, MAH stock allocation practices between countries should take into account the clinical need of patients in the Member States, such as the lack of alternatives, not just economic factors.
		7.2 The HPRA will engage with stakeholders to understand the reasons that drive stockpiling by healthcare professionals and patients and promote mechanisms that can help reduce the activity.
8	Take appropriate steps to minimise the risk of parallel trade or export exacerbating shortages	
		8.1: Companies, such as MAHs and wholesale distributors, involved in parallel trade and export should establish effective procedures whereby they do not engage in parallel trade or export activities relating to medicines subject to potential or actual shortages (e.g. checking available information such as the HPRA Shortages webpage, to establish if there is a possible supply issue with the product or clinical alternatives).

2 BACKGROUND

The World Health Organization recognises medicine shortages as a global problem. While medicine shortages have been a global issue for some time, they have increasingly affected Ireland and other European countries, significantly affecting patient care and total healthcare costs. In 2018, the Health Products Regulatory Authority (HPRA) took on a coordinating role in managing and preventing medicines shortages. As part of this, the HPRA developed a framework to facilitate a consistent and aligned approach to managing medicines shortages in conjunction with other stakeholders. The medicine shortages framework ('the framework') was generated following a review of current practices in Ireland and other countries, other published frameworks for managing medicine shortages and consultation with representatives of healthcare professionals, patients, industry, state agencies and academics. In September 2018, following the agreement with supply-chain stakeholders, the framework went live along with the associated webpage on the HPRA website, listing current and resolved medium and high-impact shortages.

This report documents the key trends observed and the main findings during the first two calendar years of the framework operation, 2019 and 2020. Although the framework was implemented before the twin challenges of Brexit and COVID-19, it provided a basis for responding to these challenges. The experience of both challenges has further demonstrated the need for continued meaningful interaction between regulators and actors in the supply chain to ensure the continued supply of medicines. This includes collaborative working with the health system, patients and the public.

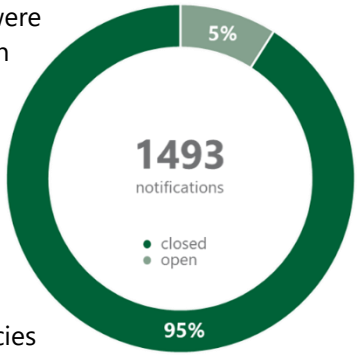
During the initial stages of the shortages framework, generally, the focus of coordinating a response to shortages has been on finding solutions once unavailability occurs. The pandemic experience illustrates that early communication and collective approaches pay off. Ireland did not experience the same shortage impact as other European colleagues during the pandemic. This was primarily driven by the close communication and aligned strategies among the HPRA, healthcare professionals, the Health Service Executive, and the pharmaceutical industry to ensure patient supply. In preparations for Brexit with industry, via the HPRA's activities and in conjunction with the HSE and Department of Health via the Medicines Criticality Assessment Group, it demonstrated the benefit of understanding more detailed information about the complex structure of manufacturing and supply chains. This is important in understanding the impact of global activities on the potential disruption to the supply of medicines to patients and elucidating pragmatic shortage responses and preventative strategies.

The report identifies further actions that should be taken to manage medicines shortages when they occur and minimise their impact on patients. It also recommends several measures to help prevent medicines shortages based on observed causes of shortages while noting that it will not be possible to prevent all shortages.

3 MEDICINE SHORTAGES – WHERE ARE WE AFTER 2 YEARS?

3.1 Notifications

For the two years in review, 1493 notifications were received, with an average notification rate of 62 per month. 3% of the total notifications received were found not to be actual medicine shortages following review. Examples of such cases include:



- situations where the item was not a medicinal product and therefore outside the scope of the framework,
- inefficient allocations (where sufficient stock is available to meet the needs of patients but supply is managed to ensure appropriate distribution) to the suitable locations at the right time based on clinical need,
- communication of inaccurate information on stock levels to pharmacies (e.g. where IT systems suggest that a medicine is out of stock when it is actually in stock) and
- situations where the medicine was available but not supplied to a patient because their pharmacy had not ordered the product in the first instance.

As of April 2021, 95% of shortage cases (potential or actual shortages) reported to the HPRA were resolved due to the resumption of supply, the prevention of the shortage in the first instance or, for a minority of cases, the discontinuation of the product.

As illustrated in Figure 1, there was an upward trend in reporting shortages during 2019, which was at least partially due to increased awareness of the framework. There was significant fluctuation during the first part of 2020, notably around the time when the COVID-19 pandemic first hit. Despite the pandemic's challenges, notifications reduced by 11% in 2020 compared to 2019, and the average number of notifications per month fell from 66 in 2019 to 58 in 2020.

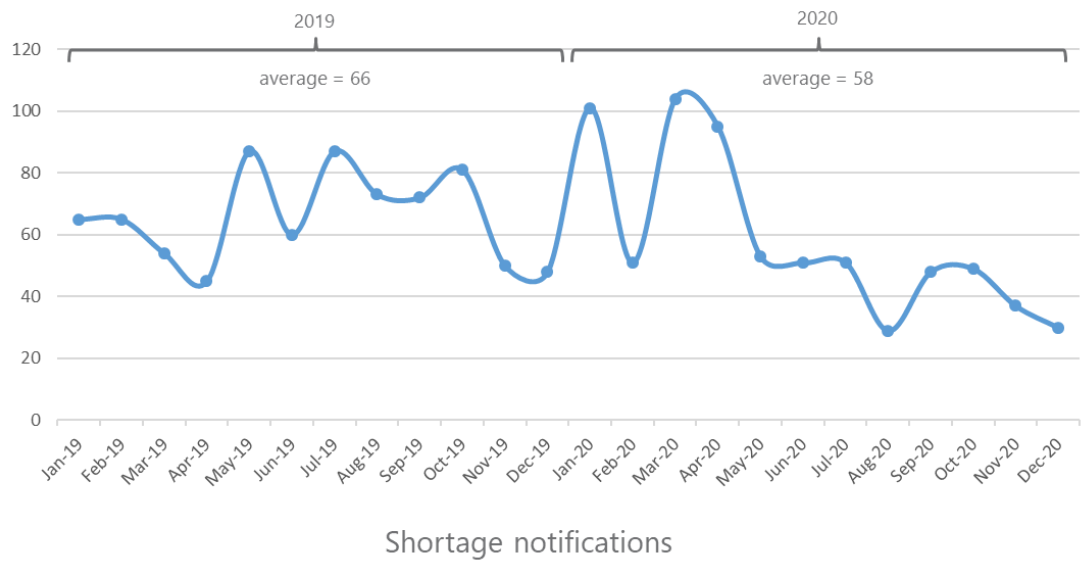


Figure 1: Monthly notifications received during 2019 and 2020. The total average notification across the two years was 62 per month.

The HPRA receives shortage notifications from various stakeholders in the supply chain. Marketing Authorisation Holders (MAHs) accounted for the majority of notifications, 85%, indicating a significant MAH engagement level in the framework (Figure 2). Other sources of notifications include other departments within the HPRA and wholesale distributors. Healthcare professionals (HCPs) and patients were the sources of notifications in 5% of cases (4% and 1%, respectively). While this demonstrates other stakeholders engaged with the framework, it also highlights an opportunity for improvement. When the first notification of a shortage comes from healthcare professionals or patients, the shortage has already occurred and was not previously reported by industry stakeholders.

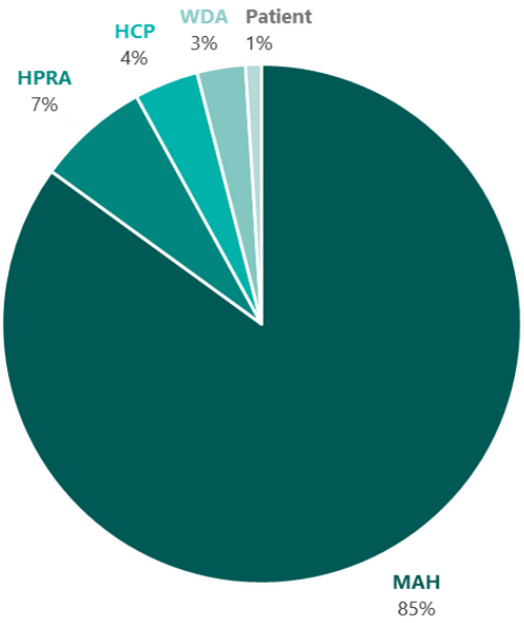


Figure 2: Source of notifications. MAH: marketing authorisation holder; HCP: healthcare professional; WDA: wholesale distribution authorisation holder.

Manufacturers are not represented as notifiers, but importantly, they may identify manufacturing issues affecting product availability earlier than most other stakeholders.

3.2 Impact status and duration

MAHs are expected to provide an impact assessment for a potential or actual shortage as part of the notification to the HPRA. During the validation phase, the HPRA also considers the anticipated impact of the shortage according to the framework parameters. The impact assessment classifies medicine shortages into three types: low, medium and high impact, based on the following key considerations.

- availability of therapeutic alternatives and
- expected impact on patients.

Figure 3 illustrates that in most cases, shortages had a medium impact (59% of cases), with low-impact shortages accounting for 22% of the cases. While high-impact shortages were less frequent (19% of cases), such shortages by their nature can be more complex to resolve and significantly affect patient treatment.

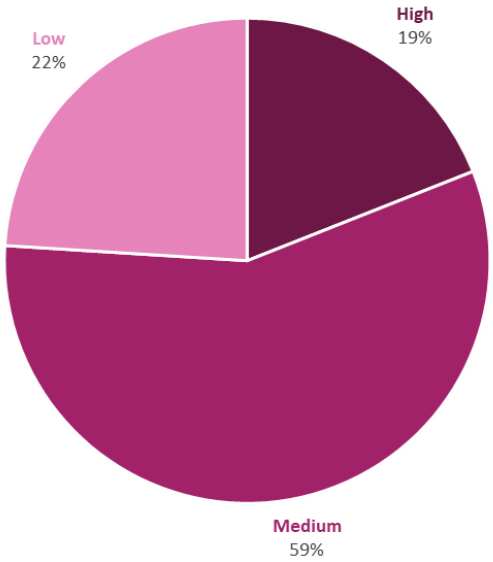


Figure 3: Impact status of shortages from 2019 to 2020

The impact assessment was not provided for 29% of the notifications, either at the time of submission or subsequently. For 64% of notifications received that contained an impact assessment, the HPRA's impact assessment agreed with the company's impact assessment. This is beneficial as it means that both the HPRA and the MAH have a common understanding of the nature of the shortage and the required input needed to prevent it or mitigate its impact. In 36% of cases, the HPRA did not agree with MAH's initial impact assessment, although subsequently, in most cases, following discussions, an agreed impact status was assigned. The consequence is that the effect of medicine not being available to patients and healthcare professionals is initially underestimated. In some cases, where the company initially inaccurately identified a shortage as low impact, the notification of the potential shortage to the HPRA took place later, closer to the start of the actual shortage. This reduces the time available to respond to and either prevent or mitigate the shortage.

There were two main reasons MAHs and the HPRA reached different conclusions about the impact of a shortage. In the first instance, the impact assigned by the reporting MAH was based on assumptions about alternative suppliers' ability to be in a position to increase the supply of their medicines to cover the shortage. These assumptions were not always valid. In several cases, the alternative supplier could not supply sufficient stock to cover the shortage. Even if the alternative supplier could cover the shortage in the short term, they could not maintain an adequate supply of their product to meet the increased demand without sufficient advanced notice.

The second reason related to the companies' approach when assigning the impact of a potential shortage was not consistent with that described in the framework. In many cases, the potential impact of a shortage was considered lower by the MAH based on actions taken to

reduce the duration of the shortage (such as expedited release or transportation of new stock). While such measures could reduce the duration of the shortage, they would not ensure continuity of supply for patients and would mean that a suitable alternative would need to be found. In some cases, companies considered their market share in the context of all products containing the same active ingredient without considering the significance of differences in the strength or pharmaceutical forms from the healthcare professional or patient perspective. To illustrate, switching a patient to an oral tablet is not always appropriate if the oral liquid form is in short supply. Additionally, some companies considered the impact in the context of all available treatments for a condition (e.g. ATC class) without considering the clinical and practical implications of changing a patient's medicine on the patient or their healthcare professional. Increasing the impact assessment's accuracy is discussed as a potential framework optimisation in section 4.3.

The average duration of a shortage was just under three months (89 days; Figure 4). When broken down by assigned impact status, the average duration of high-impact shortages (97 days) was higher than the average, reflecting the complexity of such shortages and their resolution. Despite the pandemic, there was an overall reduction of 31% in the average shortage duration in 2020 compared to 2019. The average length of a high-impact shortage was significantly halved to 63 days in 2020 compared to 118 days in 2019 (47% reduction).

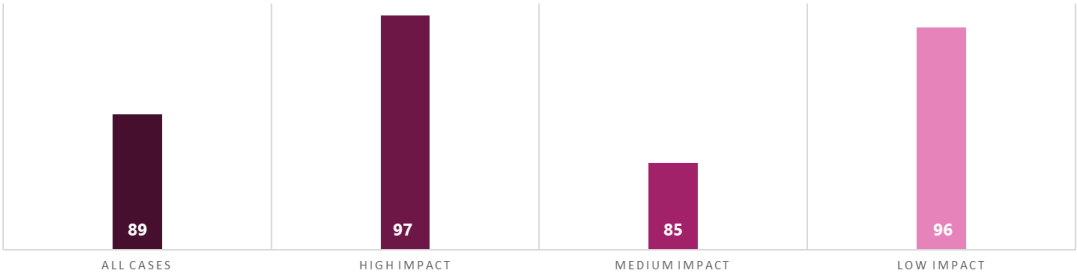


Figure 4: Average duration of a shortage (days) from 2019 to 2020 data

3.3 Timing of notifications

A crucial aspect of setting out the shortages framework is communicating a potential or actual shortage. In particular, the timely notification of an actual or potential medicine shortage is central to the operation of an effective system that aims to prevent or reduce the impact of such shortages. The framework sets out a stratified system for notification timing based on proportionate risk and aims to reduce administrative burden. While the HPRA consistently asks companies to notify a potential shortage as far in advance as possible, the notification of a confirmed low-impact shortage is required at least one month in advance. For medium and high-impact shortages, the framework sets out that potential shortages should be notified as soon as possible, at least two months in advance of the possible shortage and, mainly, when it is known that the shortage will occur. Figure 5 illustrates the range of timing of notifications received by the HPRA, where the red indicates receipt after the shortage impact, green

beforehand, and the vertically dashed line indicates a month before the shortage, where at a minimum, low-impact shortages are required to be notified.

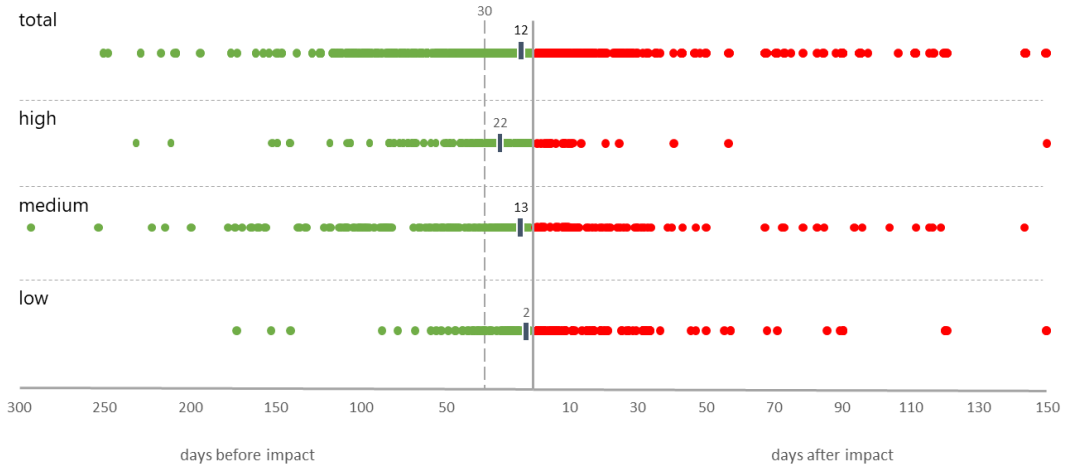


Figure 5: Timing of shortage notifications received from 2019 to 2020. Total refers to all shortages; high, medium and low refer to the stratification of the shortage according to the assigned impact. The dotted vertical line represents a timeframe 30 days in advance of a shortage occurring. The average number of days before a shortage that a notification was received is indicated by **I**. The solid vertical line (Day 0) refers to the day on which the shortage occurs. The green dots represent notifications received in advance of the shortage occurring, whereas the red dots refer to those received after the shortage occurred.

While the majority of notifications were received before the shortage began, a significant number of shortages were only notified to the HPRA after the shortage had occurred. As discussed above, shortage notifications should be submitted as early as possible and in advance of the shortage actually happening. However, the data illustrates that the average timeframe for submitting shortage notifications during the two years under review was just 12 days in advance of the shortage occurring. This significantly limited the time available for stakeholders to prevent or mitigate the impact of the shortage.

This is a particular concern for high-impact shortages that, on average, were only notified 22 days in advance of occurrence. In the case of low-impact shortages, despite the already reduced notification burden of 30 days before an actual shortage, notifications were only received on average two days before the shortage occurred. An additional concern (referred to in Section 2.2) is that where the MAH incorrectly rated the impact as low (rather than medium or high) and did not notify the shortage promptly, there was minimal time available to mitigate the effects of the shortage on patients. A key focus of the next steps in optimising the framework to prevent or reduce the effects of shortages is the early notification of potential or expected shortages (see Section 4.1).

Notification of a shortage by the MAH after it occurs means that it has already affected patients before the HPRA and other stakeholders have had an opportunity to consider the shortage and any actions that can be taken to avoid it or limit its impact.

Early notification of potential or expected shortages has benefits for multiple stakeholders and, in essence, facilitates prevention and, where prevention is not possible, mitigation. Some benefits of early notification are outlined below.

- Equips **the HPRA** with information to coordinate the management of the shortage. For example, an early notification can facilitate any necessary resources to exert regulatory flexibility, such as expedited Batch Specific Requests or Controlled Drug Import licences. Additionally, it enables communication of information with patients, alerting healthcare professionals to emerging issues and communicating with industry stakeholders about the issues.
- Provides **the HSE** with up-to-date information so that decisions can be made about, for example, the issuance of temporary reimbursement codes.
- It allows the HPRA to engage with the HSE enabling **appropriate national clinical programmes and specialist groups** to generate and distribute clinical guidance as needed, particularly in high-impact shortages. Additionally, knowledge of a shortage in advance enables appropriate prescribing of alternatives in advance. It allows pharmacists to identify sources, obtain alternatives and establish any additional clinical advice so patients can receive treatment.
- It enables alternative **MAHs** to be alerted sooner so that they are equipped to deal with increased orders and increase their products' production.
- **Wholesale distributors** can prepare for an increased activity, such as allocating resources to the receipt of additional stock, sourcing alternative medicines and activating systems to ensure equitable distribution of medicines.

Whilst each of the benefits mentioned above are useful for stakeholders, the benefit is ultimately to **patients** where the combined actions of stakeholders can either prevent a shortage or reduce its impact.

3.4 Product formulations and therapeutic categories of medicines impacted

The most common product type for which shortages were reported were oral solid dose formulations (Figure 6). This was not unexpected as the majority of medicines supplied to the Irish market are of this type.

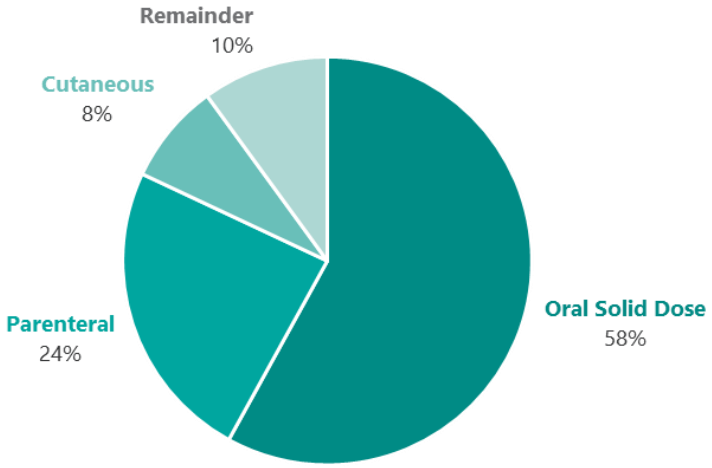


Figure 6: Formulation of products notified during 2019 and 2020

Shortages affected most therapeutic categories of medicines. The most common types affected were central nervous system (CNS), cardiovascular, anti-infectives, oncology and musculoskeletal treatments (Figure 7); these therapeutic categories represented 85% of all shortages. A point to note is that the number of shortages in a given therapeutic category could be a function of the frequency of use of those products in the hospital and community setting.

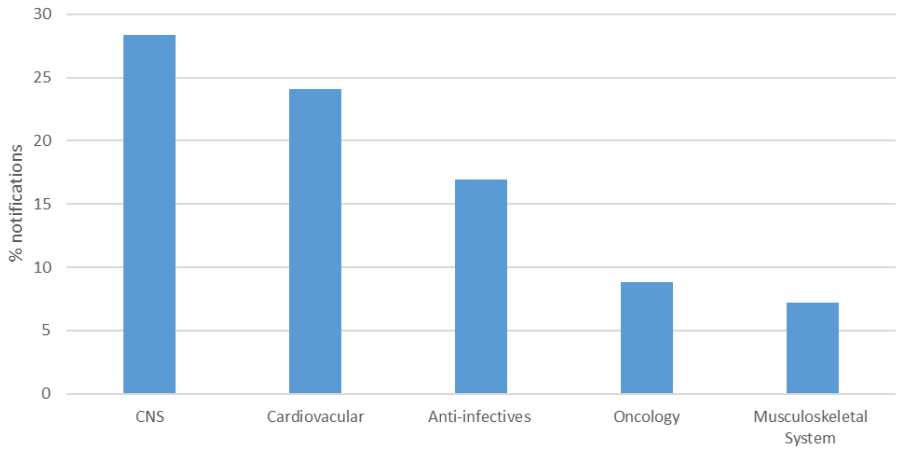
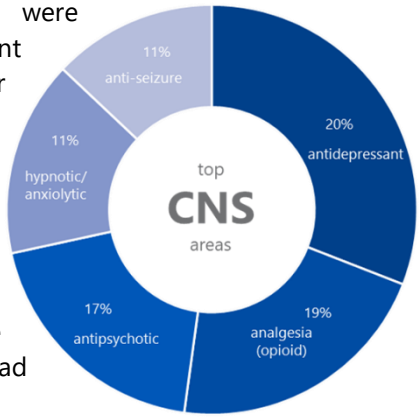
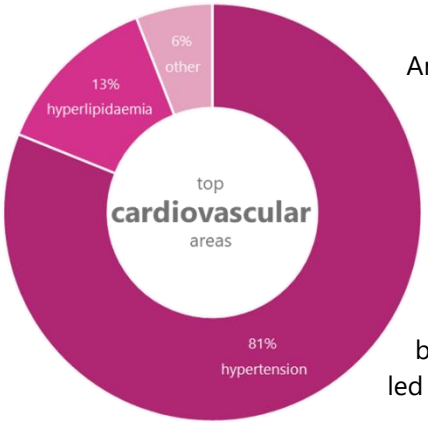


Figure 7: Therapeutic areas affected by shortages from 2019 to 2020

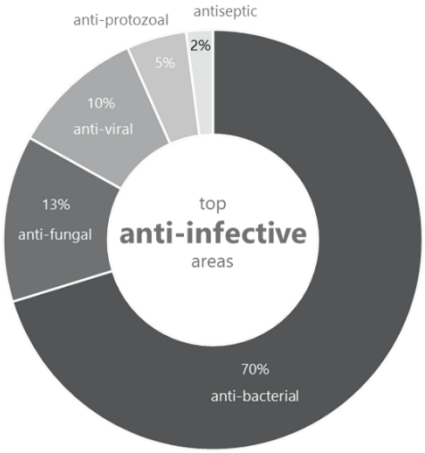
Within the CNS area, most medicines impacted by a shortage were antidepressants (20%). Whilst alternatives exist for most antidepressant medicines, it is not always easy to switch between these when a particular active substance is affected by a shortage. Analgesia (19%) and, in particular, opioid analgesics were a close second. Opioid analgesic shortages have the added complexity of being controlled drugs subject to the requirements of the Misuse of Drugs framework. The logistics of transporting these medicines from one country to another are tightly controlled. In these cases, shortages can occur due to delays in applying for licences to export from one country and import into Ireland. The remainder of the CNS categories impacted were relatively evenly spread across antipsychotic, hypnotic/anxiolytic and anti-seizure medicines.

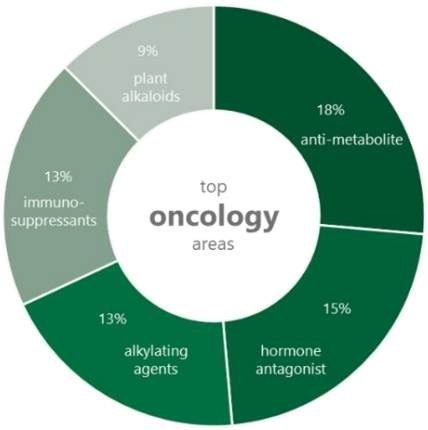




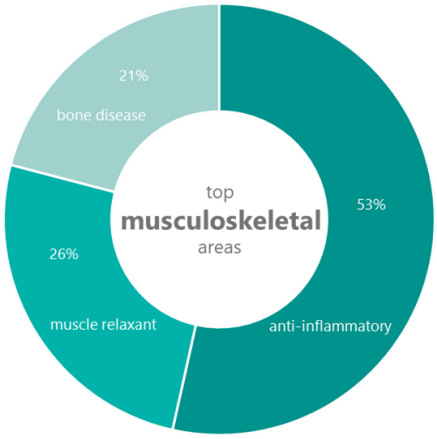
Anti-hypertensives were the most common category of cardiovascular medicine affected by a shortage (81%). This should be taken in the context of both the volume of patients prescribed medicines to treat hypertension and several high-profile issues involving the sartan group of medicines that took place during the period under review. This, in turn, resulted in large numbers of patients switching to other types of medicines, such as beta-blockers and angiotensin receptor antagonists, which also led to shortages of medicines in these groups.

The majority of anti-infectives that were in short supply were anti-bacterial products (70%). Some of the products impacted were widely used medicines and reasons for shortages included active substance shortages (e.g. piperacillin/tazobactam), resulting in a shift of a relatively large cohort of patients to alternative anti-bacterials.





Oncology medicines were also relatively evenly impacted across the range. Changes in the patterns of use of oncology medicines during the COVID-19 pandemic may also have been a factor here.



Shortages in the musculoskeletal therapeutic category were relatively evenly spread across three areas. Concerning the impact on patients, it is of interest that the majority of the anti-inflammatory medicines impacted were non-steroidal anti-inflammatories, frequently used to treat pain.

3.5 Reasons for shortages

As part of every notification of a shortage, MAHs are requested to specify the reason for the shortage. This allows the HPRA and other stakeholders to better understand the specific supply issues to determine the viability of any proposed mitigation measures to prevent a shortage. For example, a quality issue at an active substance manufacturing site could limit the availability of the active substance for many suppliers, reducing the likelihood that alternative suppliers can meet an increased demand to cover the shortage. Figure 8 illustrates the overall breakdown of reported reasons for shortages.

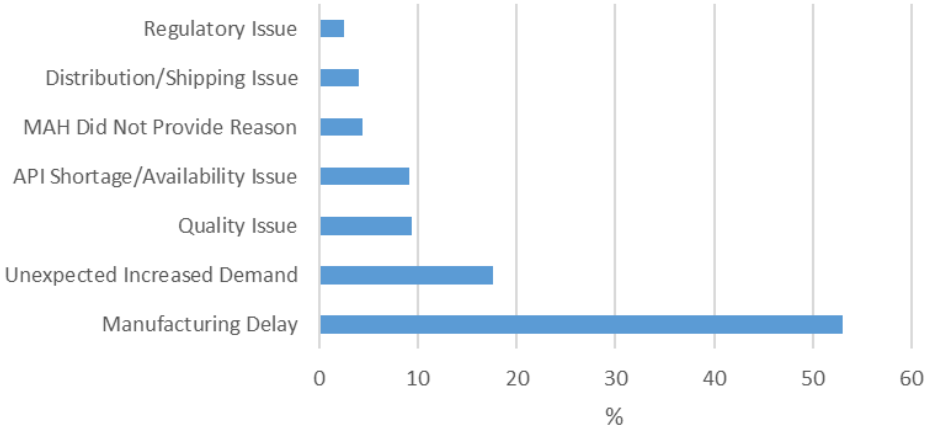
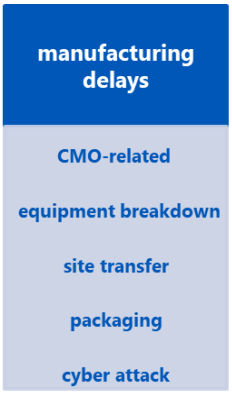


Figure 8: Reasons for shortages 2019-2020

The MAH did not provide a reason for the shortage in all cases, which reduces the likelihood of successfully preventing or mitigating the impact of the shortage.

Manufacturing delays accounted for over 50% of shortages. Often the stated reason was 'manufacturing delay' without further context. As with the situation where the MAH does not provide a reason, it is difficult to fully ascertain the extent of the shortage and the viability of possible solutions without further context. This also increases the frequency of follow-up requests from the HPRA to the company seeking additional information.



Manufacturing delays were attributed to issues with contract manufacturing organisations (CMOs). This included delays in the material receipt, capacity issues and missing production schedules. In general, many of the general manufacturing issues were reflected in matters related to CMOs. Other illustrative examples of issues that caused manufacturing delays included errors in ordering, equipment breakdown, processing delays and integrating new equipment. Although accounting for a small number of shortages, cyber-attacks can significantly impact the entire IT system of a company, which causes temporary site closures and supply-chain disruption. Manufacturing site transfers can also be linked to manufacturing delays. Often, there was little or no buffer stock to bridge the gap between the old site ceasing production and the new site becoming operational.

Given the nature of these issues, manufacturers and MAHs could implement several strategies to reduce the frequency of shortages due to manufacturing delays (see Section 6.1).

Quality issues related to quality defects and recalls (QDR) and other issues that did not result in a recall but prevented medicines from being released onto the market, such as sterility issues (e.g. isolator qualification failure) and out-of-specification results. Where shortages are due to quality issues, it can be difficult to estimate accurate timeframes for the resumption of regular supply. In many cases, identifying the root cause(s), implementing corrective actions and subsequent release of new stock onto the market can take considerable time.

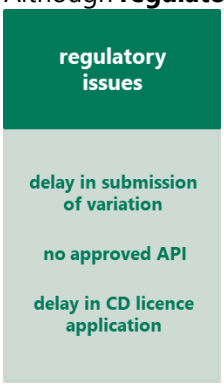
Many quality issues are attributed to manufacturing activities, although quality issues in wholesale distributors have also impacted shortages. Strategies to reduce quality-related causes of shortages are likely to reduce the number of manufacturing-related shortages (see Section 6.2).

The category of **unexpected increased demand** is likely always to be a feature of shortages. Shortages cannot always be predicted; therefore, there will be a corresponding unexpected increased demand for alternatives. Significant unexpected events (such as the COVID-19 pandemic) can significantly increase demand within a short timeframe, possibly putting pressure on existing supplies.

In many cases, this category was linked to shortages of other products in other categories. For example, if a supplier's product was in short supply due to a quality issue, there was increased demand for the competitor's product. This is similar to recalling a particular MAH's product and the inevitable switch to an alternative.

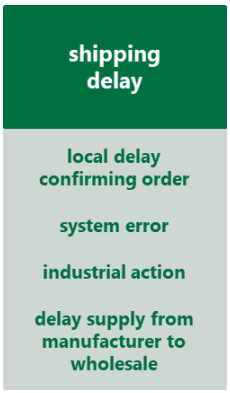
In some cases, where a higher strength of medicine was short, companies needed to consider the possibility of the lower strength going short due to increased usage of the lower strength to cover the shortage of the higher strength. It was surprising that the need to consider this had to be highlighted to some companies. Communication of the issues, particularly regarding notification and timing, is likely to prove the best tool to ensure other suppliers in the market are not surprised by an unexpected increased demand (see Section 6.5).

Although **regulatory issues** accounted for less than 5% of shortages, some crucial points were noted (see Section 6.3 for proposed prevention strategies). Delays in submission of a variation to the marketing authorisation were the main reason attributed to these issues. The delay in submission of a variation had the consequence that the product could not be released to the market, pending approval of the variation. Understanding the reasons for delays in the submission will be important to prevent these issues from happening in the future. Some cases will require closer collaboration between regulatory and supply chain functions within organisations.



An unexpected event sometimes resulted in the approved active substance supplier no longer providing the active substance. Having a viable alternative active substance supplier registered in the marketing authorisation dossier that can be activated within a short timeframe could reduce the impact and length of a shortage. As discussed earlier, medicines incorporating controlled drugs that are also subject to Misuse of Drugs controls are subject to additional regulatory requirements. Licences for the import and export of controlled drugs are routinely issued by all countries. Nonetheless, where there are delays in applying for a licence, this can ultimately lead to delays in supplying these medicines to patients. In many cases, by their nature, controlled drugs are clinically important ones, used to treat pain or in surgery, with the consequence being that shortages of this category of medicines are likely to have a significant impact, particularly in hospitals.

Like regulatory issues, **shipping delays** account for less than 5% of shortages reported to the HPRA. Of significance, however, is that these shortages were due to avoidable issues such as a local delay in confirming an order. The other main reason reported to HPRA under this category was delayed supply from a manufacturer to a wholesaler. While these may seem like logistical issues, they have directly resulted in short supply and impacted patients. A factor in this is where there is no or inadequate buffer stock to allow for any logistical issues that arise during medicines' transportation. It is acknowledged that sometimes delays in supply can result from an unexpected problem, such as a strike at ports; however, without proper contingencies, the just-in-time model contributes to the likelihood of shortages. Section 6.4 outlines strategies for shortage prevention relating to shipping delays.



The following sub-sections analyse the reasons for and types of products affected by shortages based on the three possible impact levels (high, medium and low).

3.5.1 High-impact shortages

High-impact shortages accounted for 19% of cases with an average duration of 97 days. The profile of high-impact shortages is provided in Figure 9. The main reason for high-impact shortages was manufacturing delays, which accounted for just over 40%.

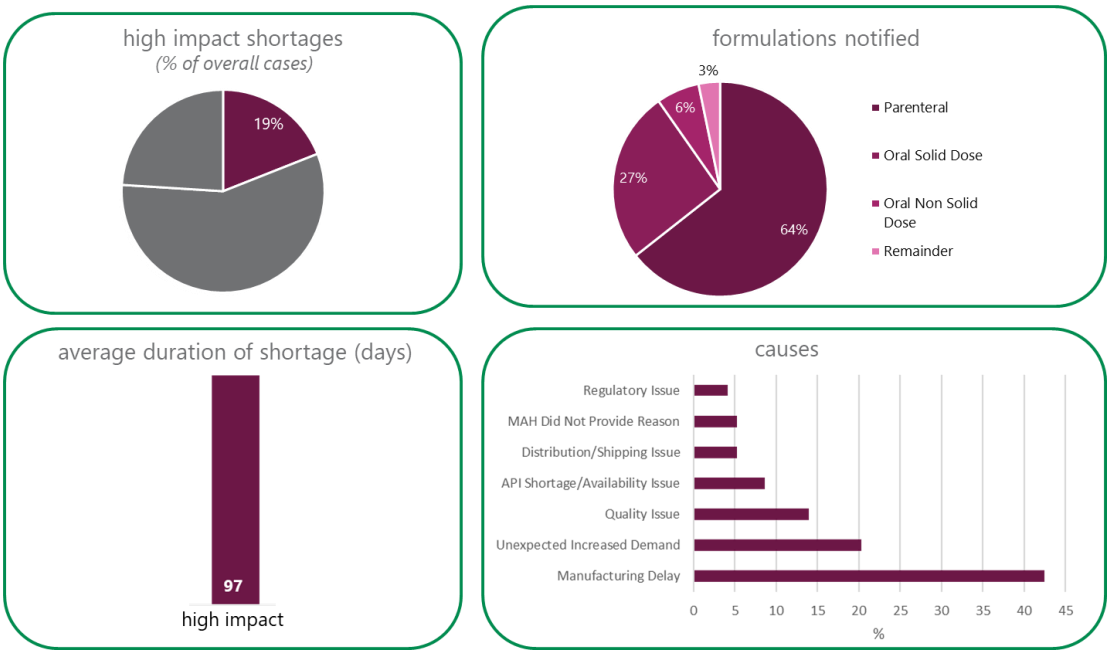


Figure 9: Profile of high-impact shortages during 2019 and 2020

Parenteral formulations accounted for 64% of high-impact shortages, with oral solid dosage forms accounting for 27% of these shortages. This contrasts with the main overall trends where solid oral dose medicines are the most common dosage forms affected by shortages.

Profile of a high-impact shortage: high impact shortages are commonly parenteral products where manufacturing delays are the main reason, lasting on average 97 days and are notified on average 22 days in advance.

3.5.2 Medium impact shortages

Medium impact shortages accounted for 59% of cases with an average duration of 85 days. The reasons for medium-impact shortages are provided in Figure 10. The main reason for medium-impact shortages was manufacturing delays, accounting for nearly 50% of these shortages.

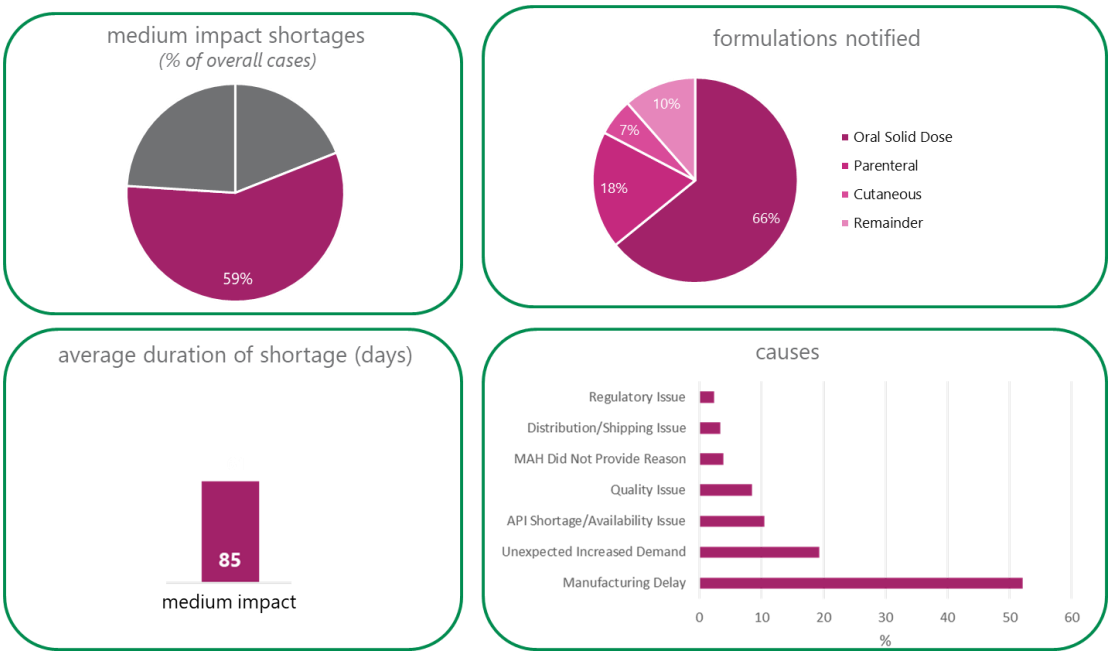


Figure 10: Profile of medium impact shortages from 2019 to 2020

Solid oral dose formulations accounted for 66% of medium-impact shortages, with parenteral formulations accounting for 18% of these shortages.

Profile of a medium-impact shortage: medium-impact shortages are commonly solid oral dose products where manufacturing delays are the main reason, lasting on average 85 days and are notified on average 13 days in advance.

3.5.3 Low-impact shortages

Low-impact shortages accounted for 22% of cases with an average duration of 96 days. The reasons for low-impact shortages are provided in Figure 11. The main reason for a low-impact shortage was manufacturing delays, which accounted for close to 66%. Of note, given that these are low-impact shortages and that they have not previously been published on the HPRA webpage, unexpected increased demand does not seem to be a significant cause of these shortages.

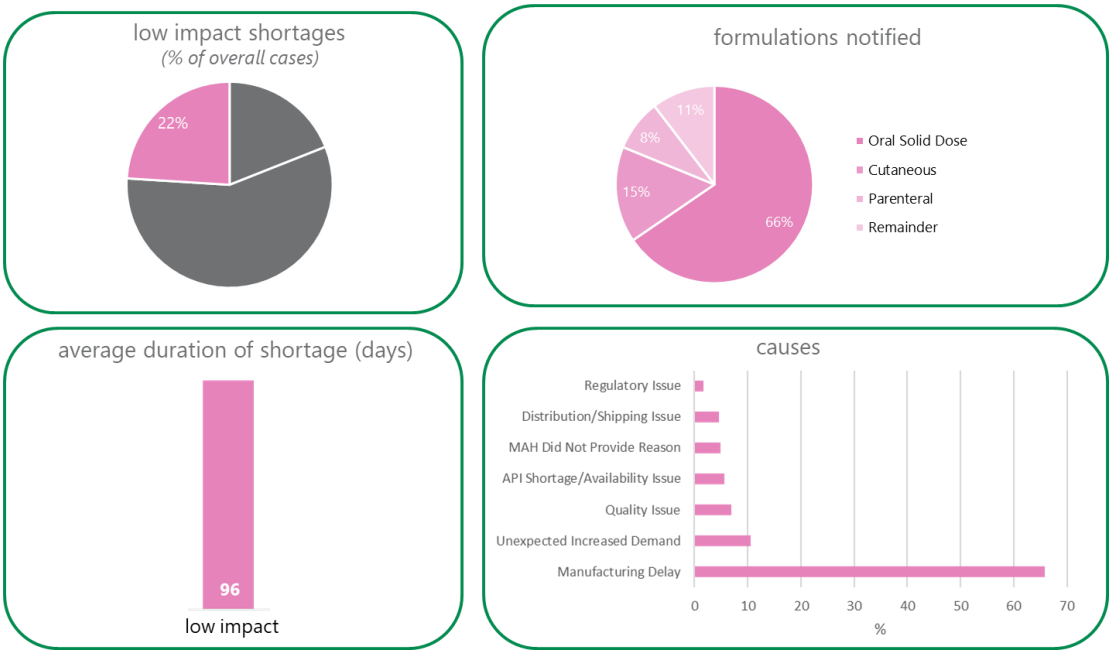


Figure 11: Profile of low-impact shortages 2019-2020

Solid oral dose formulations accounted for 66% of low-impact shortages, with cutaneous products accounting for 15%.

Profile of a low-impact shortage: low-impact shortages are commonly solid oral dose products where manufacturing delays are the main reason, lasting on average 96 days and are notified two days in advance.

3.5.4 Summary

The most commonly notified shortage profile is a solid oral dose medicine linked to a manufacturing delay. Solid oral dose medicines being the most affected by shortage could be a function of the volume of medicinal products supplied to patients. Parenteral products are the most common high-impact shortage when the types of products are stratified according to impact status. Given what parenteral products are used for, it is unsurprising that shortages of this formulation would be a high impact.

The most common reason for a shortage across all impact statuses is a manufacturing delay based on the reported details. The dynamics of the pharmaceutical supply chain mean that there has been significant global consolidation over time, notably within the manufacturing and active substance production sectors, thereby reducing the potential to find and secure alternate suppliers. Continual improvements as technology develops, updating facilities, and scientific advances are also significant factors in ensuring a resilient supply chain. The non-

implementation of continual enhancements can lead to shortages, particularly of older medicines.

3.6 Influence of the Shortages Framework

Although the multi-stakeholder framework has been live since September 2018, the influence of the framework has been seen across all stakeholders. The communication networks that have been established have facilitated the sharing of information between stakeholders as appropriate. One of the key aspects to improve this further will be earlier notifications from stakeholders of potential or expected shortages. As discussed earlier, if a pharmacist or patient has been the first person to report the shortage to the HPRA, it means that the shortage has already occurred. This limits the potential to identify and implement actions to mitigate the impact of the shortage or limit its duration.

Figure 12 illustrates the influence of the framework over the first two years. All stakeholders have worked together to reduce the impact where possible, and in 18% of cases, the shortage was prevented. Actions taken by various stakeholders include MAHs expediting deliveries, wholesale distributors prioritising quality checks and making the medicines available to order for healthcare professionals as soon as possible, pharmacists ensuring equitable distribution to patients and patients not requesting more medicines than they actually need. In 2% of cases, the products were discontinued; these became permanently unavailable due to the company withdrawing them from the market, forcing a permanent prescription change.

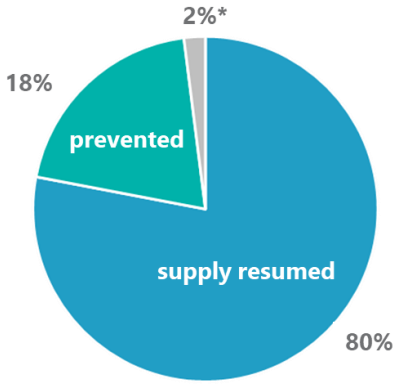


Figure 12: Influence of the shortages framework on the supply of medicines from 2019 to 2020. Asterisk denotes products that were discontinued.

Concerning the resumption of supply, a further breakdown of the data (Figure 13) illustrates that in 57% of cases where the shortage occurred, supply resumed earlier than or as anticipated. However, in 43% of cases, supply resumption occurred later than the company had initially estimated. This is important because accurate timeframes for the resumption of supply are essential in ensuring the effective implementation of mitigating measures and allowing healthcare professionals to plan for patient care.

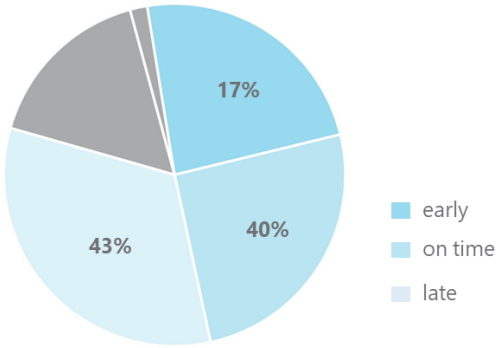


Figure 13: Further breakdown of 'supply resumption' data, representing the proportion of cases where resupply was early, on time or late. Grey sections indicate prevented or discontinued information as per Figure 13.

As with the improvements observed in reducing the number of shortages and their duration, year-on-year, there is a similar improvement in the resupply timing. The percentage of cases where supply happened earlier than anticipated improved 5% in 2020, coupled with a 3% reduction in cases where resupply was later than expected. Additionally, 2% more shortages were prevented in 2020 compared to 2019.

4 MAPPING CAUSAL AND EXACERBATING FACTORS TO THE SUPPLY CHAIN

Based on the data from this two-year review, five overarching categories for causes of shortages have been identified. Additionally, three categories of exacerbating factors have been detected. Whilst an exacerbating factor is not always a cause of a shortage, its presence can reduce the effectiveness of prevention or mitigation measures.

Figure 14 illustrates how the causes and exacerbating factors map to the supply chain. Based on the data from the review, most of the causal factors related to shortages tend to relate to the earlier stages in the supply chain (as illustrated on the left of Figure 14), and such issues are more likely to affect supply to multiple countries. Exacerbating factors are generally more prevalent at later points within the supply chain (as illustrated on the right of Figure 14) closer to the point where the medicine is supplied to the patient.

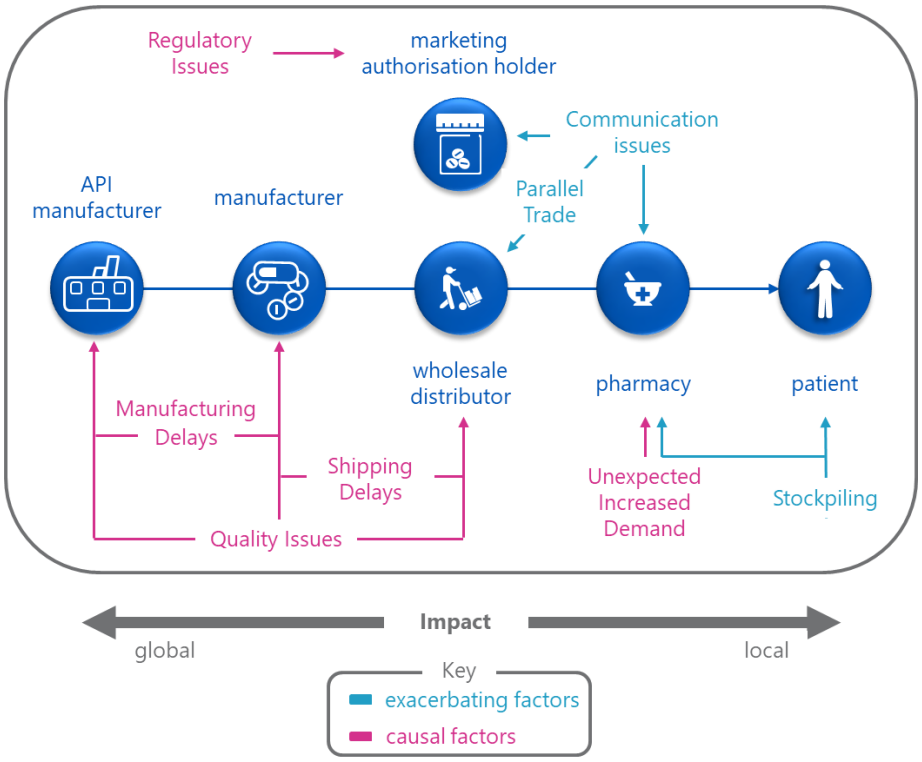


Figure 14: Reported causes of shortages and exacerbating factors mapped to the supply chain (2019 to 2020).

The following sections outline proposals and recommendations ultimately aimed at reducing the number of shortages and, where this is not possible, reducing their impact. This will be done by optimising the framework (Section 5) and identifying preventative strategies (Section 6) fundamentally linked directly to the causal and exacerbating factors.

5 OPTIMISATION OF THE SHORTAGE FRAMEWORK

This review provides an opportunity to review the operation of the framework based on experience to date and identify improvements that could be made to optimise its function.

Recommendation 1: Actors in the supply chain, such as MAHs, manufacturers and wholesalers, should notify the HPRA of a potential or actual shortage as soon as possible in advance of any shortage.

The average timing of a shortage notification to the HPRA is 11 days before its occurrence. The difficulties that this presents and the benefits of early notification to all stakeholders have been described previously in this document (Section 3.1). MAHs and wholesale distributors, in particular, are key stakeholders in the supply chain that have more visibility of stock levels than others. These stakeholders must report potential shortages at an early stage. If action is

successfully taken at an early stage to avoid the shortage or any impact on patients and healthcare professionals, then no other action is required under the framework.

Implementation action 1.1: The HPRA will engage with stakeholders to understand barriers to earlier notifications to encourage timely notifications. This will include the potential for developing alternative notification mechanisms (e.g. an Excel file). The current notification template will be updated to explicitly advise that the initial notification of a potential shortage can be the minimum details, with additional information to be provided as a follow-up.

Recommendation 2: Increase transparency relating to shortage information.

Currently, the HPRA shortage webpage lists all medium and high-impact shortages reported to the HPRA. A strategy to facilitate increased transparency is that the HPRA will publish details of low-impact shortages affecting supply to the market. As discussed in other sections of this document (see Sections 3.3 and 3.5), increased communication and knowledge sharing across different stakeholders helps to mitigate and prevent shortages. Healthcare professionals can need additional time to identify and source alternative medicines. Additionally, in an information vacuum, confusion and, subsequently, concern can lead to stockpiling of medicines and unnecessary duplication of efforts to determine a product's availability and reason for a shortage. While the HPRA is not responsible for sourcing medicines, increasing transparency will help identify the available products and alternatives.

The HPRA acknowledges that not all potential shortages will end up as actual shortages and the timing of a shortage publication is considered before publishing to its website, to preclude unnecessary worry and incorrect information. As per the Shortages Framework, the intention of publication is to inform stakeholders of the shortage and help ensure that the impact is mitigated. This requires that where confirmed shortages occur, the publication of these will be proportionately in advance of the actual shortage. Considering the effect of a low-impact shortage and subsequent proportionality of response, these shortages will be published on the start date of the confirmed shortage, whereas medium and high-impact shortages will be published in advance, where possible.

An additional aspect is that given the global nature of the supply chain, there is a need to collectively engage and develop closer relationships with European and international partners to facilitate coordinated actions about medicines supply. The Heads of Medicines Agencies and the European Medicines Agency's current work on the availability of medicines has already resulted in developing an information-sharing and communication platform among regulatory authorities relating to shortages in their markets[1].

[1] The establishment of the medicine shortages single point of contact working party (SPOC WP) network has improved medicine shortage information sharing between Member States, the EMA and the European Commission and coordinated actions to help prevent and manage shortages. More information on the Taskforce is available here.

Implementation action 2.1: The HPRA will publish confirmed low-impact shortages.

Implementation action 2.2: The HPRA will develop case studies to improve stakeholders' understanding of the role of the HPRA in the coordination of management of shortages and the approach that is taken to prevent potential shortages or mitigate their impact.

Implementation action 2.3: The HPRA will continue to promote the development of international cooperation, thereby increasing information sharing and transparency, which will optimise the national shortages framework.

Recommendation 3: MAHs should increase the accuracy of notification detail provided to the HPRA.

An essential step in the framework operation is for the HPRA to receive key information about a potential shortage. It is important that notifications provide all information requested in the form to enable the HPRA to understand the current situation, assess the impact and consider prevention or mitigation measures so that all stakeholders, as needed, have time to react.

Based on the data collected for this review (Sections 3.1, 3.3 and 3.5), some critical pieces of information are often missing from notifications or not fully completed. As described earlier, not elucidating the specific manufacturing delays means that it is difficult to understand the impact and evaluate the likely timeframe for the resumption of supply. Additionally, understanding if a shortage will affect Ireland or other countries is important, as this would assist in accurately determining the impact (including possible implications for the supply of other similar medicines) and understanding the options available to mitigate or prevent the shortage. For example, an issue that affects Ireland only may have solutions via the Batch Specific Request mechanism if the medicine is available in other countries.

Increasing the accuracy of the initial MAH impact assessment will also ensure a cohesive response to a shortage. The inaccurate assessment of an issue as a low impact may have consequences on a company's internal processes, not least for the time point at which the HPRA is notified. Furthermore, in several cases, the impact assessment and possible mitigation measures have not been provided by the company, thereby resulting in delays in implementing potential options to prevent or mitigate the impact of a shortage.

Implementation action 3.1: The HPRA will engage with stakeholders directly to further develop the notification process, host training sessions for industry notifiers, and develop practical guidance for completing the notification form based on the engagement outcomes.

6 PREVENTATIVE AND MITIGATING STRATEGIES

The preventative strategies outlined here are aimed at the underlying causes of shortages. They would ensure that shortage prevention is actively considered part of the medicine's lifecycle

management. Additionally, many of the causal factors appear to have overlapping aspects that lend themselves to being addressed by more than one preventative strategy. One example would be the 'unexpected increased demand' category, where often, an issue with the supply of one product will affect the availability of alternatives. The underlying factors for unexpected increased demand include shortages and recalls; targeting the other four categories likely has a positive impact on this causal factor.

Complementary to the recommendations outlined below is the European Commission's Pharmaceutical Strategy, which includes a specific intention to address medicine shortages as part of its four main pillars. The global nature of the medicine supply chain will require more international collaboration and alignment to ensure the security of medicine supplies and shortage prevention. The Commission aims to put forward legislative and non-legislative proposals to address medicine shortages, including preventative and mitigation strategies. The HPRA's involvement in the Pharmaceutical Committee, the Commission's Structured Dialogue, and other activities relating to the Pharmaceutical Strategy will support the implementation of the recommendations outlined below on an international level.

In presenting the preventative and mitigation strategies, the HPRA seeks stakeholder support in implementing the recommendations. The general intention is to optimise and harness all information sources and intelligence available in a pre-emptive rather than a reactive way. Appropriate implementation of preventative strategies benefits patients and health systems in either ensuring continued supply or being prepared to mitigate the impact of a shortage should it occur. For industry, preventative strategies will have benefits, including concerning certainties of outcomes.

Recommendation 4: Optimise pharmaceutical quality systems to strengthen the reliability and resilience of supply chains throughout the lifecycle of a medicine

It is apparent from the data gathered that failures associated with pharmaceutical quality systems contribute to many shortages. While the current Good Manufacturing and Distribution Practices (GxPs) set out practically a minimum standard for quality, there is a need to shift the paradigm and focus of the industry to achieve an increased supply chain resilience that reduces the burden of shortages.

As the medicine regulatory system adapts to new demands, focus on continual improvement of pharmaceutical quality systems and post-authorisaiton change processes to strengthen the reliability and resilience of supply chains is needed, thereby enabling prevention of shortages where these areas are the root cause.

Implementation action 4.1: Industry stakeholders should support continual optimisation of the pharmaceutical quality system to strengthen the reliability and resilience of the medicine supply chain, thereby enabling better prevention of shortages.

Implementation action 4.2: The HPRA will continue to engage with the medicine regulatory network to promote mechanisms whereby optimisation of the regulatory processes can contribute to enabling better reliability and resilience of supply chains, thereby enabling better prevention of shortages.

Recommendation 5: Increase resilience in the supply chain, taking into account known vulnerabilities

Pharmaceutical supply chains are complex and often fragmented and involve many hand-overs throughout the supply chain before dispensing to a patient in the pharmacy. While consolidated global supply chains offer efficiencies, some aspects are more vulnerable to disruption, leading to shortages. Based on the two-year review, this has been demonstrated by the number of shortages related to shipping delays coupled with a lack of contingencies.

In an unexpected disruption during the manufacture of medicines, it is often not possible to increase production to restore depleted stocks at short notice due to lead times or pre-determined production schedules, particularly at CMO facilities. Suppose this happens for a medicine where no account was made for potential fluctuations in the supply chain. In that case, there is little redundancy to cover the shortfall of medicine flow, and shortages are likely.

Based on the information available, on average, there are between six and eight weeks' worth of stock of many medicines at the primary wholesale level with a further two weeks at secondary wholesale. This, however, is not the case for all medicines. A disruption to a manufacturing activity for medicines where companies did not account for potential fluctuations in the supply chain, for example, could result in a delay in the replenishment of stocks that could quickly lead to the depletion of the available stock and shortages. Multiple confounding factors could also elevate the risk of shortages if coinciding, including a shortage of a similar medicine or unexpected increased ordering by the public and healthcare professionals. Where this product is a controlled drug, the speed at which products can be imported is affected by international controlled drug licensing requirements, further reducing the potential to mitigate the effect of a shortage. Based on the information gathered over the two years, some shortages could have been prevented if adequate preparation had allowed for possible transportation delays from manufacturers to wholesalers and ultimately to pharmacies.

Issues linked to transfers of manufacturing activities to different sites caused several shortages reported to the HPRA. In general, there was not enough or, in some cases, any contingency stock available to prevent a shortage when a problem arose during the site transfer.

Implementation action 5.1: Companies should ensure that they consider the potential for fluctuations in the supply chain, particularly for medicines with limited clinical alternatives, given the potential for high-impact shortages.

Implementation action 5.2: MAHs and manufacturers should ensure enough buffer stock to allow for unexpected delays during manufacturing site changes or ownership transfers.

Recommendation 6: Improve communication between stakeholders

The single biggest issue that has resulted in difficulties during the management of shortages is sub-optimal communication (either inadequate or inaccurate). This presented itself most starkly regarding the lack of timely communication to the HPRA of potential or actual shortages (see Figure 6). However, it was not restricted to this – other examples related to ordering delays and local delays in confirming an order resulted in shortages. Additionally, based on the data available, in some cases, weeks can pass between a problem identified at a manufacturer and the communication with MAHs. The introductory chapter to the GMP Guide implies the need for cooperation between the MAH and manufacturer and the need for two-way communication systems to be in place between them. This cooperation should be extended to communication relating to potential or actual shortages.

Several points in the supply chain could benefit from increased communication, particularly given the medicine supply chain's complex nature. Illustrative examples include:

- Intra-company communication between different departments, such as commercial and regulatory functions. Such communication allows the information gathered by those who have visibility on supply at wholesale and pharmacy level to be shared with regulatory colleagues and vice-versa to identify potential issues early and take actions to prevent any impact on supply. We have observed that where companies have increased internal communications, such as between commercial and regulatory colleagues, this has resulted in better quality communication with the HPRA and an increased ability to prevent and mitigate shortages.
- Communication between the local MAH representative in a member state and the manufacturer should be expedited where potential supply problems are identified.
- Wholesale distributors can identify supply issues, for example, by observing low stock levels or identifying increased product orders. In some cases that have arisen, shortages could have been prevented if the reduction in stock levels had been identified earlier and a system was in place to respond effectively by placing an order with the MAH or the primary wholesaler.
- Information about stock levels may be available to healthcare professionals via ordering portals. While this can be helpful, if the information is incorrect (e.g. a medicine is presented as being out of stock instead of on allocation), this can lead to confusion and unnecessary use of the shortages framework.
- Significant changes to national or local hospital treatment protocols or new public health measures could result in clinical practice changes, thereby causing unexpectedly increased demand. It may leave little time for the MAH to update its production and forecasting for the immediate and long-term to ensure continued supplies.

The benefits of communication, including notification to the HPRA, enable all stakeholders to be better prepared to prevent the shortage from occurring or, at worst, mitigate its impact.

Implementation action 6.1: Each stakeholder should continue to establish effective and frequent communication between the different actors such as within the different teams or affiliates of the MAH as well as between the MAH, the relevant manufacturing sites and the wholesaler.

Implementation action 6.2: Stakeholders involved in developing clinical treatment or public health measures should consider the impact of such changes on demand for some medicines. Where there is a potential for a significantly increased demand for individual medicines, arrangements should be made to communicate this to suppliers to enable them to adjust supply accordingly.

Recommendation 7: Promote fair and equitable distribution to meet the needs of patients

The stockpiling of medicines results in a disrupted supply chain. Stockpiling can prolong the duration of a shortage, precipitate a shortage or result in an inequitable distribution to patients. To illustrate, in one case observed during the period under review, five months' worth of stock of one clinically important medicine was depleted from wholesale distributors in one month, leading to a shortage. This was despite the company's additional stock being made available in response to the increased demand. This meant that available supply was not fairly distributed to all pharmacies and consequently to patients that needed it.

In another instance, where a potential shortage was anticipated but should have been prevented if all stakeholders ordered their normal quantities, a significant increase in orders was observed following communication of the possible shortage leading to quicker than expected depletion of the available stock and an actual shortage

Implementation action 7.1: Stakeholders should not order or dispense more stock than normal where there is a potential or actual shortage. This has the effect of creating a supply issue where there may not have been one. Additionally, in a shortage, MAH stock allocation practices between countries should consider the clinical need of patients in the Member States, such as the lack of alternatives, not just economic factors.

Implementation action 7.2: The HPRA will engage with stakeholders to understand the reasons that drive stockpiling by healthcare professionals and patients and promote mechanisms that can help reduce the activity.

Recommendation 8: Take appropriate steps to minimise the risk of parallel trade or export exacerbating shortages

Parallel trade is the activity of supplying medicines intended for patients in one country to another country. The free movement of medicines is a legitimate business practice. It depends on several factors, including arbitrage and, more recently, demand from non-EEA-based companies. When a shortage of medicine occurs, the medicine supply is insufficient to meet patients' needs. Although the supply of medicines outside of the State is unlikely to cause a

shortage, it can contribute to worsening the extent of a shortage. Where the shortage of a medicinal product significantly affects patients and health systems, it is vital to ensure that the supply of that medicine to patients in the State is maintained for as long as possible to minimise the clinical impact on patients.

Implementation action 8.1: Companies, such as MAHs and wholesale distributors, involved in parallel trade and export should establish effective procedures whereby they do not engage in parallel trade or export activities relating to medicines subject to potential or actual shortages (e.g. checking available information such as the HPRA Shortages webpage, to establish if there is a possible supply issue with the product or clinical alternatives).

7 CONCLUDING REMARKS

The development and implementation of the multi-stakeholder framework for handling shortages have been the first step in the national response to shortages. A direct consequence has been gathering comprehensive data on the nature of shortages observed in the Irish market for the first time. This review has identified several strategies that can serve as the foundation for the next phase of the framework, further developing the management of shortages and driving the implementation of preventative strategies. There is a need to optimise the notifications of potential and actual shortages, including earlier submission of notifications in advance of potential shortages and improving the accuracy of the detail provided to maximise the opportunities to prevent potential shortages from being realised or limiting their impact. There are also pathways to address the challenge of preventing shortages and further mitigating their impact, aiming to tackle the causes and exacerbating factors. These include increasing supply chain resilience and improving communications.

Recent events such as the COVID-19 pandemic, Brexit and other geopolitical events have further highlighted many international challenges in ensuring supply of medicines. These challenges and the importance of addressing medicines shortages have been recognised across the EU and more globally, and additional steps are being taken to tackle shortages. Complementary to the strategies outlined in this review, the international initiatives tackling the complexities of shortages include:

- the European Commission's Pharmaceutical Strategy, where part of the work focuses on improving supply chain resilience,
- the joint task force of the Heads of Medicine Agency and European Medicines Agency (EMA) on the availability of medicines, which will progress strategies aimed at shortage prevention,
- the further development of the European Medicinal Product Single Point of Contact (SPOC) Working Group, which has facilitated greater communication on shortages that may impact multiple countries,
- the introduction of legislation to expand the remit of the EMA to enhance coordination of shortages from an EU perspective,
- the European Joint Action on shortages and

- the inclusion of medicine shortages in the European Medicines Agencies Network Strategy to 2025.

Stakeholders' input in optimising the framework and implementing prevention strategies and mitigation measures will enable a more significant and informed Irish contribution to these international initiatives. The international initiatives can also reciprocally help to ensure that some of the recommendations of this review can be successfully implemented and have the optimum chance of success in preventing shortages.