

# The HPRA's Quality Defects and Recall (QDR) Programme - a focus on Quality Risk Management

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## HPRA's Quality Defects and Recall Programme

Investigate, on a **risk** basis, reports of suspected/confirmed quality defects in medicines and related active substances.

Make decisions about the need for recalls and other risk-mitigating actions for the Irish market, as well as other required actions (e.g. for-cause inspections).

- **Quality Defect** - an unplanned attribute of a medicinal product, or component, which may affect the **quality, safety and/or efficacy** of the product and/or which is not in line with the approved marketing authorisation/product registration file for the product or component
  - **Recall** - retrieval from the marketplace of a batch or a number of batches of a medicinal product as a result of a quality defect or a non-compliance. Retrieval of a batch or batches is considered a recall once the batch(es) has been QP released and left the site of the manufacturer that QP released the batch(es) to the Irish market
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# Quality Risk Management & the QDR programme

**QRM is the core principal underpinning the QDR programme in the HPRA.**

**Risk-based Decision Making** runs through all aspects of the QDR processes.

(based on ICH Q9, as well as Chapter 8 of the EU GMP Guide)

Includes decisions about the potential risks that the defect issue may pose to patients and animals, the classification of the defect issue (Critical, Major, Minor, Non-Justified), and also includes decisions about:

- Prioritising QDR cases for work – over 2100 reports were received in 2021
  - Whether market action is needed and what level of market action is commensurate with the level of risk
  - Whether cessation of product supply/recall action may be inappropriate, given product shortage considerations
  - Adequacy of the company's root cause analysis and proposed CAPAs
  - Whether a for-cause inspection is needed
  - Whether additional/increased regulatory oversight needs to be applied to the manufacturer or the MAH as a result of the QDR issue
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# Quality Risk Management & the QDR programme

**Risk-based Decision Making** runs through all aspects of the QDR programme

(based on ICH Q9, as well as Chapter 8 of the EU GMP Guide)

Includes  
patient  
Non-Ju

**Chapter 8 of EU GMP Guide (Complaints, Quality Defects and Product Recalls) has multiple references to risk-based decision making**

**The upcoming revision of ICH Q9 (Quality Risk Management) will provide new guidance on risk-based decision making**

- Adequacy of the company's root cause analysis and proposed CAPAs
- Whether a for-cause inspection is needed
- Whether additional/increased regulatory oversight needs to be applied to the manufacturer or the MAH as a result of the QDR issue



## Quality Risk Management cont'd

The HPRA's work on Quality Defects is also based on the **Compilation of Union Procedures** – see EC Eudralex Volume 4 webpage at this link:

[https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-4\\_en](https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-4_en)

- The Compilation is a set of procedures that each EEA medicines GMP inspectorate is expected to follow, and specifies the quality system requirements for each GMP inspectorate
- There are two quality defect-related procedures in the Compilation – these were last revised in 2021 and the revision work was led by the HPRA
  - ***Management and classification of reports of suspected quality defects in medicinal products and risk-based decision-making***
  - ***Management of rapid alerts arising from quality defects risk assessment***

Note: The procedures in the EU Compilation have an important Appendix “Guidance in relation to the risk-based classification and decision making for quality defects, recalls, rapid alerts and risk reviews” that Manufacturers and MAHs are encouraged to review.



## Risk-based Classification of Quality Defects

(New terminology – see [Compilation of Union Procedures on Inspections and Exchange of Information](#), last revised September 2021)

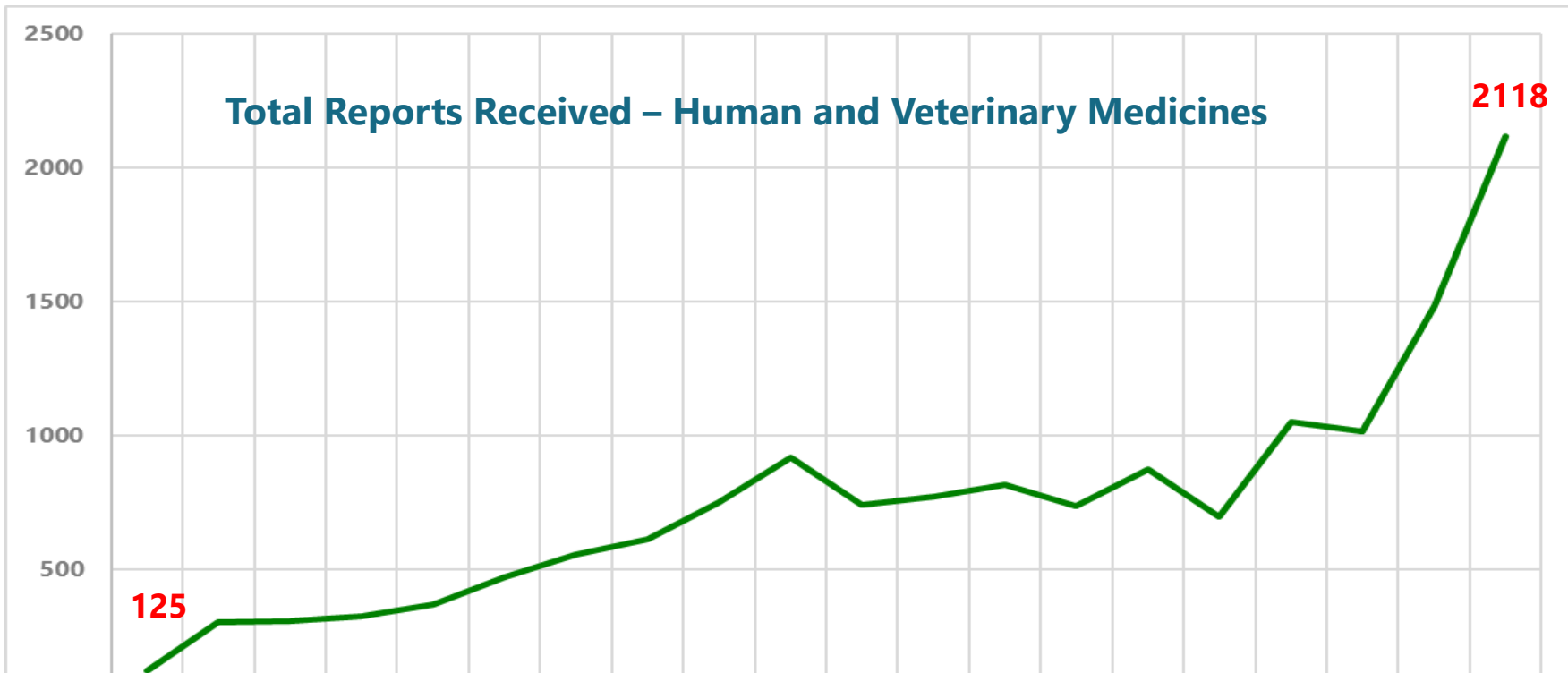
- **High Risk (Critical) quality defects** - defects which are potentially life-threatening or could cause serious risk to health e.g. particles in injectables, product mix-up, microbial contamination
- **Moderate Risk (Major) quality defects** - defects which could cause illness or mistreatment, but are not classified as critical
- **Low Risk (Minor) quality defects** - defects which are not likely to pose a significant hazard to health e.g. minor labelling issues, wrong or missing batch numbers, marginal OOS at end of shelf life

**Note:** Classification is based on potential for harm, route of administration, patient cohort, extent of defect, method of sale/supply, detectability etc...

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# Twenty years of Quality Defect Reports



Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Critical	5	40	50	66	84	173	127	105	173	231	189	235	365	213	126	129	351	269	324	408
Major	83	152	167	199	238	216	300	345	332	364	303	300	199	218	343	209	323	310	737	1416
Others	37	111	92	62	49	84	128	164	246	322	249	239	252	306	407	360	376	437	425	294
<b>Total</b>	<b>125</b>	<b>303</b>	<b>309</b>	<b>327</b>	<b>371</b>	<b>473</b>	<b>555</b>	<b>614</b>	<b>751</b>	<b>917</b>	<b>741</b>	<b>774</b>	<b>816</b>	<b>737</b>	<b>876</b>	<b>698</b>	<b>1050</b>	<b>1016</b>	<b>1486</b>	<b>2118</b>
Recalls	70	74	85	74	58	97	141	98	168	253	141	109	102	118	216	89	202	132	85	124



## Reflecting on the increase in QDR reports

- Increased reporting by manufacturers and MAHs, partly as a result of an increased focus on quality defect reporting by HPRA GMP (and GDP) Inspectors
- Increased clarity on what is reportable via more detailed guidance from the HPRA

### **Other factors include:**

- Increased globalisation of manufacturing and of supply chains in general – increased complexity, resulting in increased risks of things going wrong
  - Increased complexity in medicines packaging – esp. in the use of pen-based delivery devices for biological products – many defect reports received on those
  - Brexit – HPRA became supervisory authority for more manufacturing sites as locations of batch certification moved to Ireland...and this meant that HPRA gets directly involved in more quality defect issues involving centralised products
  - Large number of quality defect reports received for Covid-19 vaccines
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## Human Medicine Quality Defect Reports

<b>Risk Classification/Year</b>	<b>2017</b>	<b>2018</b>	<b>2019</b>	<b>2020</b>	<b>2021</b>
High Risk (Critical)	124	325	259	312	396
Moderate Risk (Major)	196	280	291	701	1381
Low Risk (Minor)	327	308	375	378	235
Reports not justified	3	12	23	17	21
<b>Total</b>	<b>650</b>	<b>925</b>	<b>948</b>	<b>1408</b>	<b>2033</b>

## Veterinary Medicine Quality Defect Reports

<b>Risk Classification/Year</b>	<b>2017</b>	<b>2018</b>	<b>2019</b>	<b>2020</b>	<b>2021</b>
High Risk (Critical)	5	26	10	12	12
Moderate Risk (Major)	13	43	19	36	35
Low Risk (Minor)	30	56	38	29	37
Reports not justified	0	0	1	1	1
<b>Total</b>	<b>48</b>	<b>125</b>	<b>68</b>	<b>78</b>	<b>85</b>



# Quality Defect Reports (2021)

<b>Who Reported?</b>	<b>Human</b>	<b>Veterinary</b>
Pharm. manufacturers, distributors and MAHs	32%	49%
Pharmacists	39%	
Other Competent Authorities	26%	51%

<b>What Was Reported?</b>	<b>Human</b>	<b>Veterinary</b>
Contamination	33% (679 cases)	9% (8 cases)
Product Preparation/Administration Issues	25% (514 cases)	
Non-compliance with Specifications	7% (133 cases)	7% (6 cases)
Stability	5% (104 cases)	44% (37 cases)
Falsification	4% (90 cases)	
Non-compliance with MA	4% (78 cases)	9% (8 cases)
SmPC/Printed Artwork	3% (64 cases)	7% (6 cases)
Non-compliance with GMP	1% (18 cases)	9% (8 cases)



## Actions Taken (2021)

<b>Recalls</b>	<b>Human</b>	<b>Veterinary</b>
Primary Wholesale	8	1
Secondary Wholesale	9	
Pharmacy/Retail/Vet	84	6
Patient/patient level action	16	
<b>TOTAL</b>	<b>117 (16 IE)</b>	<b>7 (0 IE)</b>

<b>Caution in Use Notifications etc.</b>	43	1
<b>Rapid Alert Notifications to other CAs</b>	3	0

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## Recalls (2021)

<b>Cause</b>	<b>Human</b>	<b>Veterinary</b>
Contamination issues	33	3
Validated transport time excursions	26	
Cold chain/temperature excursions	15	
Non-compliances with specifications	13	1
Stability Issues	6	1
Erroneous distribution incidents	6	
MA Non-compliances	5	1
Lack of Sterility Assurance issues	4	1
Issues with FMD Safety Features	2	
Unlicensed products on the market	2	
Other miscellaneous defect issues	5	



## 3 Rapid Alerts issued by HPRA to other Competent Authorities - 2021

- **Shedding of particulates** from a filter component in a product for infusion which had the potential for contaminate the actual product.
- **Falsified medicines** detected in a number of third country markets - the genuine products were manufactured in IE.
- **Braille readability issue** – due to the misplacement of the FMD anti-tamper device (ATD) stickers.
  - Braille non-compliance issues are frequently seen in the HPRA’s Sampling & Analysis programme e.g. low dot height, Braille not in line with the MA, wrong Braille format.
  - In 2020, 46% of the packs checked for Braille were non-compliant (18% in 2021)

### What QC checks are your QC labs doing on Braille?

- On incoming outer cartons?
- On finished packs?
- How adequate and robust are those checks?
- Are your QC labs checking against the Braille Declarations made by the MAHs to the HPRA?
- Do your QC labs know what is in those Braille Declarations?



## Top Categories of Quality Defects in 2021 (human use products **manufactured in IE**)

- Product preparation/administration Issues (31% - mainly with Pre-filled Pen & Pre-filled Syringe medicinal products, e.g. device activation failures, pre-mature activations, product leakages, jammed devices)
- Stability OOS/OOT issues (13%)
- Various product contamination issues (12%)
- MA Non-compliance Issues - CMC & Artwork (7%)
- Errors in printed artwork and in SmPCs (7%)
- Non-compliance with specifications (6%)

*e.g. Products not meeting appearance/organoleptic specs*

*Packs not meeting fill specs, empty capsules/blisters*

*Broken tablets in packs....*

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## Examples of recalls during 2021 (human use products **manufactured in IE**)

- Total Parenteral Nutrition (TPN) batches with too low a concentration of NaCl - (hospital level recall)
  - Elemental impurity above the ICH Q3D acceptable limit (wholesale level recall)
  - Cloudiness in lipid infusion products indicating a potential lack of sterility assurance (hospital level recall)
  - Validated transit time exceeded for a number of cold-chain infusion and other products (hospital level recall)
  - Azide impurity in a sartan product that was at levels exceeding the safe limit (pharmacy level recall)
  - CIU Letter & Package Leaflet not securely attached to the packs (wholesale level recall)
  - Erroneous distribution of a number of empty O<sub>2</sub> cylinders (hospital level recall)
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## Other Examples of Recent Recalls

- **March 2022:** Pharmacy-level recall of Quinapril/Hydrochlorothiazide Tablets - nitrosamine impurity at levels exceeding the safe limit
  - **Jan 2022:** Pharmacy-level recall of Cyclosporin Eye Drops – crystallised particles in the product
  - **Jan 2022:** Patient-level recall of Zinc Sulphate Capsules - 100 rogue white tablets and a rogue package leaflet being found in one pack
  - **April 2021:** Patient-level recall of two Liothyronine/Levothyroxine products - under-concentration of both actives in the tablets
  - **Nov 2020:** Hospital pharmacy-level recall of a Glucose 50% IV product - cracks in the glass vials leading to sterility assurance risks
  - **May 2020:** Recall of an Investigational Medicinal Product from a clinical trial in children - product mix-up in different arms of the trial
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Could similar quality defect issues  
occur at your manufacturing site?



## Take contamination issues for example...

- The majority of recalls in 2021 related to *contamination quality defect issues (29%)*
- And there were additional recalls due to a *lack of sterility assurance* - which is another potential route for contamination to occur
- The earlier presentation today on the HPRA's GMP Inspection programme and its deficiency findings referred in many places to contamination issues, and also to poor control over aseptic operations
  - e.g. of the 105 major deficiencies identified in *Production in 2018-2021, 30% related to deficient contamination control/cleaning validation, and a further 13% related to deficient controls for aseptic operations*
  - *And it is of note that Production and Premises & Equipment, which are important in relation to contamination controls, were the 2<sup>nd</sup> and 3<sup>rd</sup> largest areas in which major deficiencies were cited in 2018-2021.*





## EU GMP Guide Chapter 1 - Pharmaceutical Quality System states:

*"The manufacturer must manufacture medicinal products so as to ensure that they..*

- are fit for their intended use*
- comply with the requirements of the Marketing Authorisation or Clinical Trial Authorisation, as appropriate,*
- and **do not place patients at risk** due to inadequate safety, quality or efficacy."*





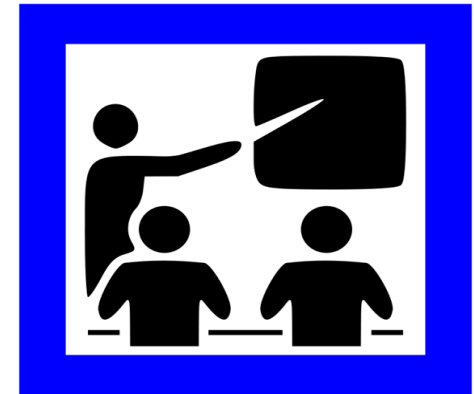
# The vast majority of Quality Defects reported to the HPRA are manufactured using...



Qualified Equipment



Validated Processes



Trained Staff



## The vast majority of Quality Defects reported to the HPRA are manufactured

**It is useful to think about the effectiveness of Quality Risk Management activities in GMP facilities at this time...**

**Why are validated manufacturing processes producing defective batches of medicines?**

**How robust has the hazard identification part of risk assessment been?**

**To what extent has risk assessment been integrated into qualification and validation activities?**

**How can true risk-based qualification and validation be achieved?**



Q

Validated Processes



## ***Contamination-related Case Study***



## Contamination Case Study

- A FP manufacturer in IE contacted the HPRA to advise that it had been notified by a filter supplier about a recall of certain lots of filters.
  - Certain lots of filters (produced on one identified cutting machine) were shedding an unusually high number of particulates  $\geq 100\mu\text{m}$ .
  - Filter supplier did not have a specification for particles, but had concluded that the particle count was high and unacceptable.
  - Particles were of three types – filter membrane material, filter housing material and cellulose.
  - The  $5\mu\text{m}$  sterile filter was co-packed in the carton of an infusion medicinal product and used to provide protection for patients against incomplete reconstitution of the product.
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## Contamination Case Study cont'd

- 22 impacted lots of the 5µm filter had been supplied to the Irish manufacturer and packed into >100 FP batches for > 40 markets.
  - No quality defect with the actual medicine inside the packs – the defect related to the filters.
  - No ADRs had been reported to the MAH which could be linked with the defect.
  - The filter particles had the potential to be infused into the patient, including paediatric cohort (from 1 month in age).
  - Probability of harm to patients was assessed as low by the manufacturer – taking into account various factors.
  - A product/batch recall would have resulted in a shortage on some markets, and in some markets, this was a critical / essential product.
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## Contamination Case Study cont'd

### Immediate Actions:

- Finished product packed with the impacted filters was placed on hold (at the manufacturing site and at primary distributors in various countries)
- Notification of the issue to the HPRA and other Competent Authorities by the FP manufacturer/MAH
- Market impact assessment & health hazard evaluation performed

### Outcomes:

- Withdrawal of the filter component from all affected FP batches in Ireland via a letter sent to hospital pharmacists - replacement non-impacted filters were supplied to them
  - Rapid Alert Issued by HPRA to other competent authorities – recalls occurred in some countries
  - For-cause inspection by HPRA at IE manufacturer
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## Key HPRA Observations about this Case

**Understanding the extent of the defect issue** - which filter lots and FP batches were affected and which markets were impacted - was complex and took time, and the company's quality system initially failed to generate/compile accurate data

- Inaccurate listings of impacted FP batches were generated and a number of impacted FP batches were omitted in error
  - Not all impacted markets were identified early on - this resulted in a number of Competent Authorities being provided with incomplete and inaccurate details of which defective FP batches were on their markets
  - At the same time, communications and risk-based decisions needed to be made about the need for risk-reducing actions in various markets (e.g. filter replacement, or pack recalls, etc.)
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## Key HPRA Observations about this Case

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**How much assurance do you have in your company's ability to accurately and quickly link specific lots of components and starting materials with FP batches and markets?**

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replacement, or pack recalls, etc.)

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## Key Observations cont'd

**Understanding the risks posed to patients by the defect was also complex** – there were many different aspects to consider – e.g. different patient cohorts, particle toxicological considerations, the potential for foreign body reactions, immunological responses, thromboembolic events. Adverse reaction reporting rates were also taken into account.

- The company performed a robust and multi-disciplinary risk assessment – it devoted considerable effort to assessing the various risks from a scientific perspective, and there was a strong emphasis on understanding the clinical risks presented by the particulate issue.
  - The risk assessment found that the issue was potentially life-threatening for paediatric patients and that it could lead to permanent impairment of body function/permanent damage to a body structure.
  - The risk assessment appeared to indicate a high reliance on detection of the particles by healthcare professionals – when this aspect was queried by the HPRA, the company clarified that this was not actually the case – the risk assessment was just somewhat unclear on this point.
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## Key Observations cont'd

**Understanding the risks posed to patients by the defect was also complex** – there were many different aspects to consider – e.g. different patient cohorts, particle toxicological considerations, the potential for foreign body reactions, immunological responses, etc. All of these aspects were also taken into account.

- The company's risk assessment process was not clear in relation to how they arrived at their risk estimates.
- The company's risk assessment processes to deliver scientifically sound risk estimates and decisions were not clear.
- The risk assessment appeared to indicate a high reliance on detection of the particles by healthcare professionals – when this aspect was queried by the HPRA, the company clarified that this was not actually the case – the risk assessment was just somewhat unclear on this point.



## Key Observations cont'd

### **The level of filter supplier oversight by the FP manufacturer had been weak.**

- No reassessment (or risk review) of the supplier had been performed following the defect issue.
    - *This was especially important with regard to the change control process in place at the supplier*
    - *The filter defect issue directly related to a change control that had been poorly assessed and managed by the supplier - the change had been assessed as minor by the supplier and had not been reported to the FP manufacturer.*
  - No consideration had been given by the FP manufacturer to assigning a more restricted status to the supplier following the incident.
  - The investigation highlighted weaknesses in the company's general management of suppliers – e.g. supplier oversight levels were almost exclusively based on supplier audit outcomes and not enough attention was paid to supplier performance between audits or to the intrinsic risks presented by the materials being supplied.
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## Key Observations cont'd

**The level of filter supplier oversight by the FP manufacturer had been weak.**

- No reassessment (or risk review) of the supplier had been performed following the def

**What kind of Risk Review processes are in place in your company with regard to suppliers?**

**Is Risk Review a formal concept in your oversight programme?**

- No rest
- The of sup  
supplier audit outcomes and not enough attention was paid to supplier performance between audits or to the intrinsic risks presented by the materials being supplied.



**Lastly, don't let MA Non-compliance issues  
trip you up...**







## MA Non-compliance Issues

### MA Non-compliances are, by definition, Quality Defects

- 86 cases in 2021 (78 human, 8 vet) – where batches that were out-of-compliance with the MA had been QP certified to the market
- In 33% of these cases, the products were manufactured in Ireland
- In 2021, 7 Recalls and 8 Caution-in-Use Notifications were required to manage the risks posed to patients and animals by these defective batches

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
<b>No. of MA Non-compliances</b>	76	85	68	77	119	72	91	64	102	86
<b>% of Total Quality Defects</b>	10%	11%	8%	7%	14%	10%	8%	6%	7%	4%
<b>CMC- related</b>	23	47	32	26	101	30	27	21	24*	41
<b>Artwork -related</b>	53	38	36	28	18	42	64	43	68*	45
<b>Recall in Ireland</b>	11	11	8	5	14	7	3	0	8	7
<b>CIUN in Ireland</b>	2	1	5	13	0	4	1	3	5	8

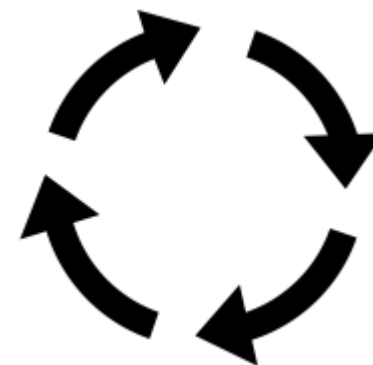
\* Approximate figures



## Reflecting on the MA Non-compliance Issues

### The same issues continue to occur year after year...

- Failures to implement variations within the required timelines (often applies to artwork-related MA changes)
  - *e.g. failures to reflect updated safety warnings in Package Leaflets*
- Failures to submit artwork variations requested by the HPRA (e.g. following PRAC safety recommendations)
- Implementing changes prior to variation submission and/or approval (mainly happens with CMC changes)
  - *e.g. resulting in the use of non-registered test methods, non-registered API manufacturers and non-registered packaging components*





## Reflecting on the MA Non-compliance Issues

### Contributory factors include:

- **Poor Manufacturer – MAH communication processes**
- **Non-robust Change Control processes which fail to prevent the issues**
- **Weak PQR processes which fail to identify all regulatory-impacting changes**

**Q: Is your company vulnerable to these issues?**

**Q: How does your company assure MA Compliance?**

**Q: As a QP, how do you ensure that you are not certifying batches that are MA non-compliant?**

**For guidance in this area, see the July 2021 Reflection Paper on MAHs & GMP - on the EMA website**

- The earlier presentation today on the HPRA's GMP Inspection programme and its deficiency findings also referred to **MA Non-compliance issues**
  - *e.g. of the 111 major PQS deficiencies in 2018-2021, 14% related to **Batch Certification/QP Oversight***
  - *And it is of note that the **PQS**, which is important in assuring MA Compliance, was the largest GMP area in which major deficiencies were cited in 2018-2021*



## Resources

- HPRA Guide to Reporting and Initial Investigation of Quality Defects in Human and Veterinary Medicinal Products, Document No. SUR-G0023
- HPRA Guide to Quality Defect Investigation Reports, Document No. SUR-G0029
- HPRA Guide to Recall of Medicinal Products for Human and Veterinary Use, Document No. SUR-G0019
- ICH Q9 Quality Risk Management - **watch out for the new revision to come out later this year**
- EU GMP Guide Chapter 8
- Reflection Paper on MAHs and GMP (EMA website)
- Compilation of Union Procedures -EC Eudralex Volume 4





**Thank you for your attention.**

**Contact us:**

Quality Defect reporting form for industry  
(SURF0180) is available on [www.hpra.ie](http://www.hpra.ie)

or

email: [qualitydefects@hpra.ie](mailto:qualitydefects@hpra.ie)

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