Complaints – Investigation and Review

Conference Document| 22nd February 2018

Adequate investigation of market complaints is important

Quality and safety

Ensure patient safety

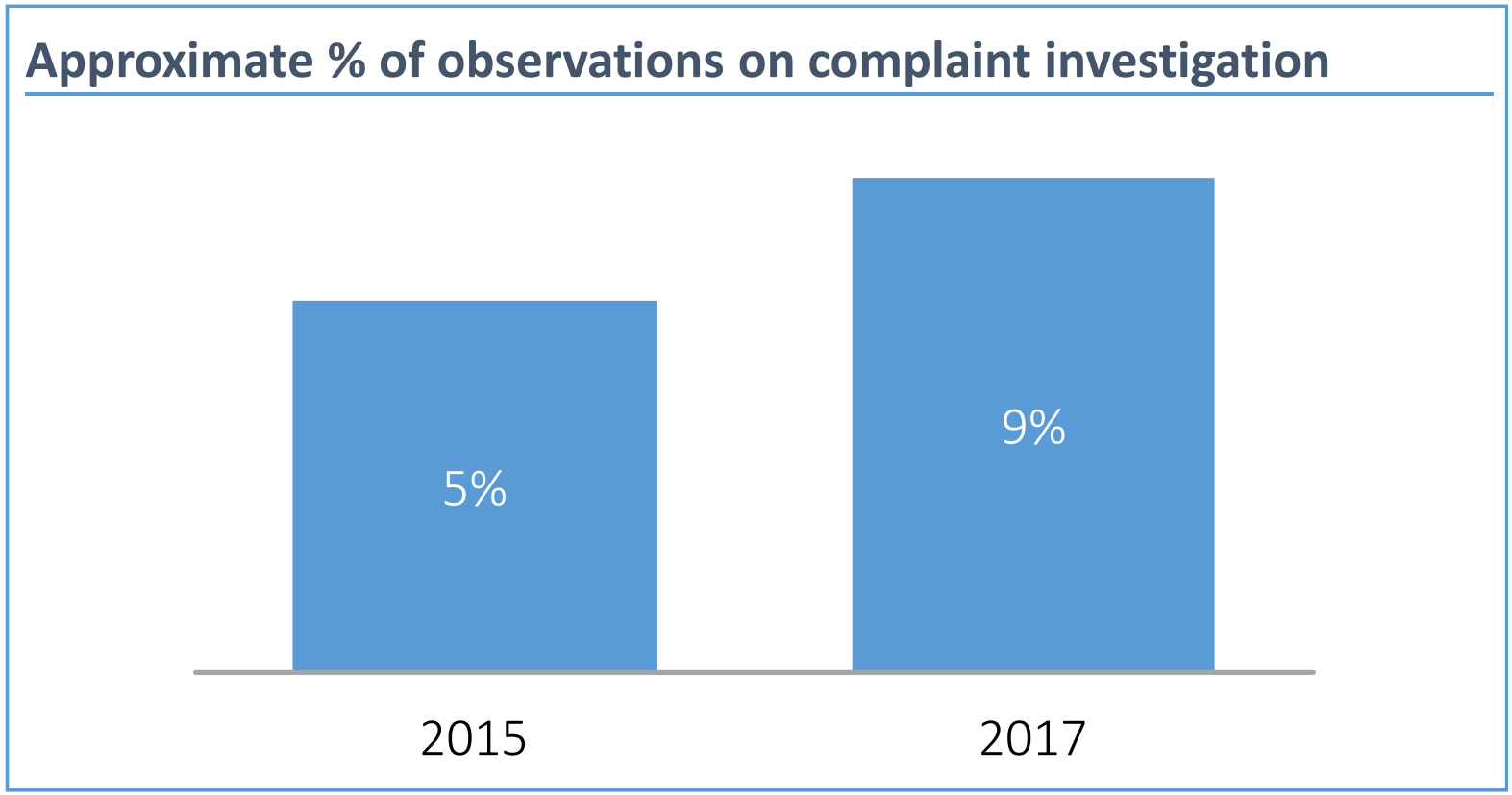
Maintain product quality

Cost

Reduce cost of poor quality

Minimize rejects & reworks in future products

Share of complaint investigation in the warning letters has been increasing over the last 2 years



1 Analysis of FDA WL from 2015-2017. Calculated as number of observations on market complaints/ total number of observations in the audit

Regulatory guidelines for complaint investigations

"Records of complaints should be retained to evaluate trends, product-related frequencies, and severity with a view to taking additional and, if appropriate, immediate corrective action"

– ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

"Quality Risk Management principles should be applied to the investigation and assessment of quality defects and to the decision-making process in relation to product recalls corrective and preventive actions and other risk-reducing actions"

– EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

"Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products"

– WHO Expert Committee on Specifications for Pharmaceutical Preparations

"A structured approach to the investigation process should be used with the objective of determining the root cause"

– ICH Harmonised Tripartite Guideline Pharmaceutical Development Q10

Further detailed out

Industry is facing 4 key challenges with market complaints

		Challenges faced by industry
1	Approach for common complaints	• Number of common complaints come up (e.g., approach to black particles on tablets) but no standard approach (e.g., SMEs) for investigation
2	Complaint investigation	• Multiple decision points where subjective judgement becomes critical – e.g., defining "repetitive" com-plaints, deciding whether complaint classifies as "high risk" or "low risk", raising a field alert report (FAR)
3	Data availability and information	• Data availability is lower compared to other investigations that happen closer to batch release/ product manufacturing
4	Learnings from complaints and failure management	• Opportunity to improve knowledge transfer and effectively embed learnings from complaints and failure management in future product development

Observation examples in audit

You must notify your customer if your firm determines that any batch of distributed drug product should be subject to a field alert report (FAR). However, there was no evidence that a notification was sent to your customer……

The investigation into this complaint concluded that the control of (b)(4), a known impurity, may be related to the odor detected, and the investigation was closed in October 2011, before the implementation of the proposed corrective actions

SOURCE: FDA warning letters from 2015 to 2017

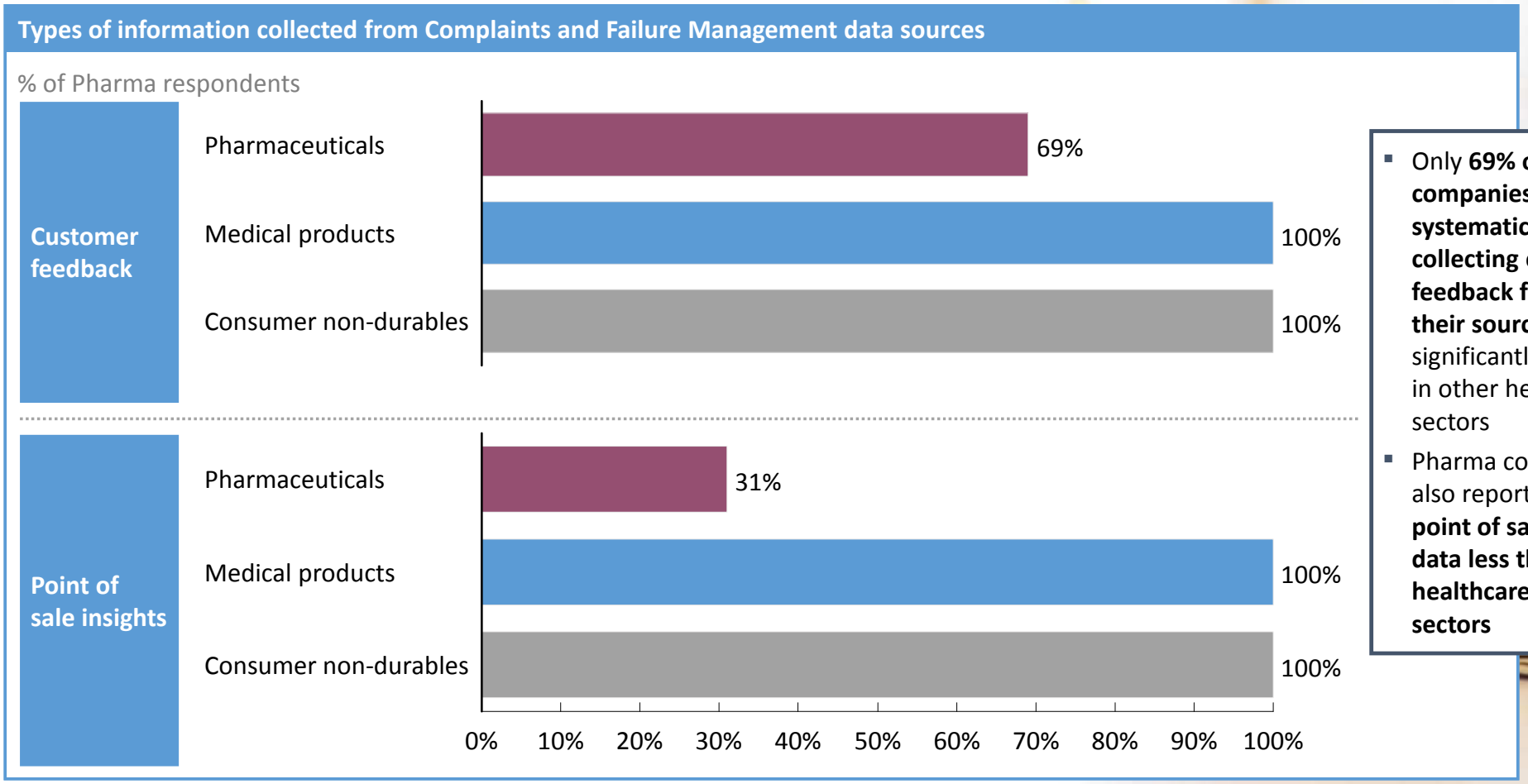
2 Pharma companies differ widely in the way they handle investigations

Salient features	A	B	C	D
Complaint categorization	• Critical, major, minor	• Medical, technical and both	• Medical, quality, chemical	• Critical, major, minor, non-substantiated
FAR	• 3 working days from notice of defect	• Based on impact assessment	• If critical, 3 working days from receipt of complaint	• Based on evaluation for FAR requirement
Timeline for closure	• 15 days from logging for critical, 30 days for non critical	• 30 calendar days	• 10 working days from receipt of complaint	• 30 working days
Approver of market complaint	• QA incharge	• Plant quality head	• CQA	• Site quality head

Significant variation occurs in complaint categorization, FAR and complaint closure timeline across pharma companies

SOURCE: Benchmarking exercise across IPA QF companies

3 Also, pharma lags behind other industries in systematically collecting customer feedback and POS insights from data sources

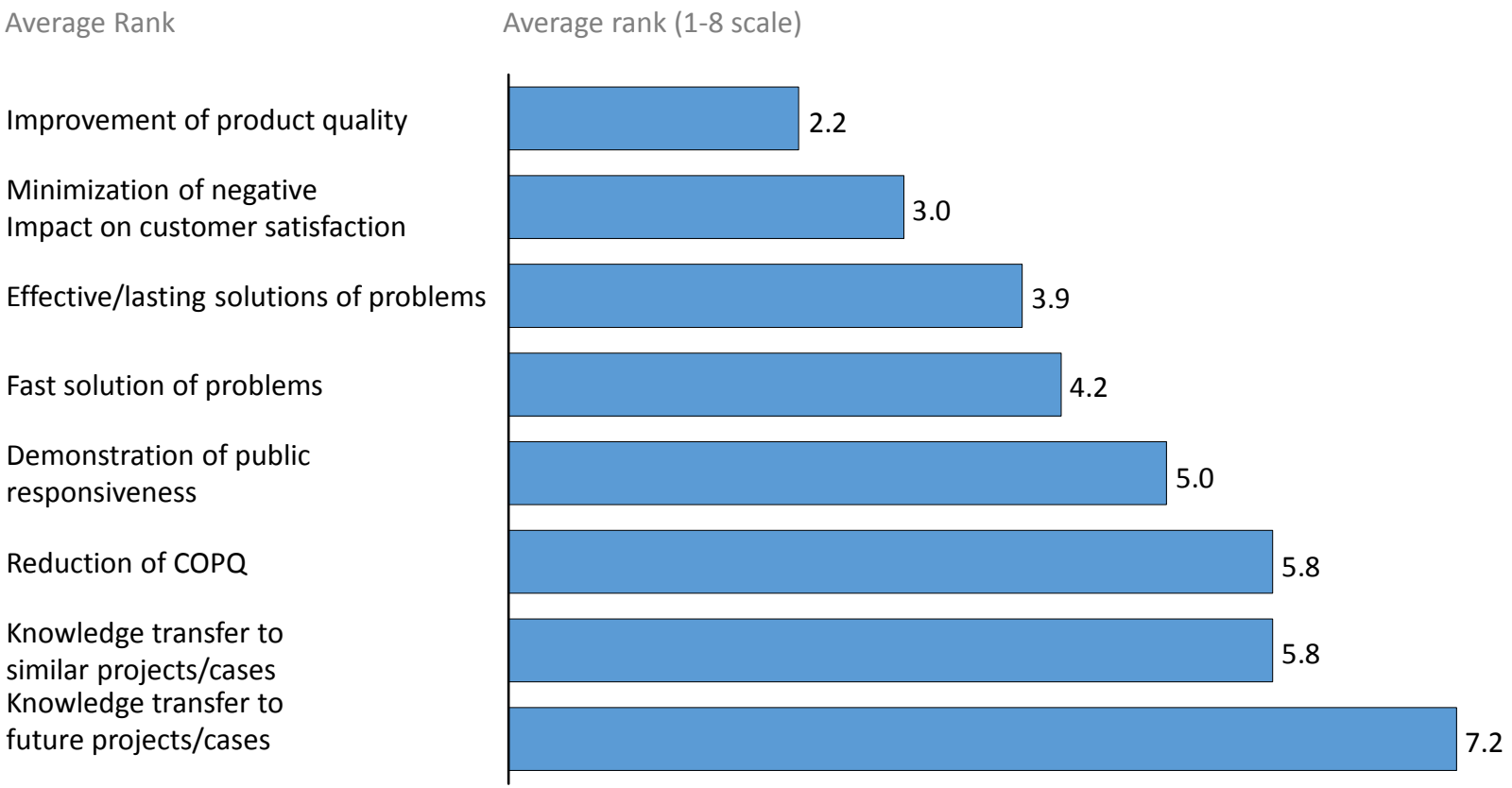


- Only **69% of pharma companies report systematically collecting customer feedback from any of their sources,** significantly less than in other healthcare sectors
- Pharma companies also report collecting **point of sale/service data less than other healthcare industry sectors**

SOURCE: Complaint & Failure Management Survey, 2016 by McKinsey and company |WZL RWTH Aachen University

4 Pharma companies can do more in embedding learnings from complaints and failure management into future product development

Pharmaceuticals priority ranking[1]



- Although companies report that improving product quality is essential, **embedding knowledge consistently ranks as low priority**
- **Pharma assigned a lower priority to knowledge transfer than most other industries**

1 Forced rank of CFM elements from 1-8 where 1=top priority and 8=last priority

SOURCE: Complaint & Failure Management Survey, 2016 by McKinsey and company |WZL RWTH Aachen University

To address these challenges, IPA QF sub-group 5 identified and worked on 3 improvement areas

	Improvement areas	Highlights
1	**Standard approach for common complaints**	• Standardized approach / criteria for responding to common issues (e.g., addressing black particle complaint) • Integrating Process Validation and complaints
2	**Best practices SOP to improve complaint investigation effectiveness**	• Standardized definition of market complaints (e.g., what complaint classifies as repetitive complaint) • Standardized approach to address LOE complaints
3	**Requirements for specific investigation**	• Established process and system requirement for different types of investigations

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Complaints – Investigation and review

Sub-group 5

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Sub-group 5 of IPA quality forum collaborated to develop best practices for complaint management

Company name	Name	Pic
Zydus Cadila	Avinash Joshi	
LUPIN	Indrajit Bose	
LUPIN	Pooja Shah	
torrent PHARMA	Dilkesh Shah	

Company name	Name	Pic
Cipla	Shiney Joy	
SUN PHARMA	Jigar Marfatia	
Dr. Reddy's	Ramakrishna Vempaty	

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Comprehensive 5 step approach was adopted to define best practices for market complaint handling

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Comprehensive scan of regulatory guidelines 01

- ICH Q9 – quality risk management
- ICH 10 – pharmaceutical quality system

Pooling best practices across QC companies 02

- SoPS of 5+ companies

Multiple Brainstorming sessions 03

- 20+ executives 15+ meetings (in person/telecom)
- 5+ discussions with CEO Panel

Validation by SMEs 04

- Sent to multiple Industrial experts

Feedback from regulatory agencies 05

- Received comments and inputs from regulatory bodies

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Guidance document was created to address the 3 focus areas identified in existing complaints investigation and review process

1. Best practice SOP

- Standardized definition of market complaints – what should be considered 'repetitive', how should we handle issues identified at EU QP etc.
- Standardized approach to address LOE complaints – criteria for considering testing of control samples, addressing 'repetitive' LOE cases etc.

2. Standard approaches to situations outside SOPs

- Standardizing approach / criteria for responding to typical/common issues
  - Approach to "Black particles on tablets" complaints
  - When do we raise an FAR vs not; especially during mix-up
  - Deciding substantiated vs unsubstantiated complaints
- Integrating Process Validation and complaints
  - Reconciliation of PV and market complaints
  - Escalation of ADEs to QA

3. "Bare-minimum" requirement for different types investigations (e.g., LOE)

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Guidance document consists of 3 areas to standardize the approach to complaints management across the industry

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Best practice document on complaints and investigation management

1

Overall guidance on handling of complaints for drug product

Generalized procedure for end-to-end handling of market complaints of drug products by standardizing approach for responding to typical/common issues as well as situations outside SOPs

2

Dosage form wise checklists defining investigation criteria for market complaints

Checklists to define bare minimum requirement and investigation criteria for dosage form specific complaints (product quality or packaging related complaints), for e.g., OSD, Ophthal, PFS, black particles & LOE related complaints

3

Guidance document on risk assessment for complaint investigation

Generalized procedure to establish a criteria for raising FAR and/or subsequent product recall for substantiated complaints based on their severity, frequency of occurrence and detectability

The output document will add to existing knowledge in the industry:

- Provides practical guidance and support on how to do different types of investigations
- Covers new dosage forms where collective knowledge is limited
- Harmonizes and captures internal best practice

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1

Salient features of SOPs from different companies were discussed and debated to identify best practice

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Salient features discussed

- Login and acknowledgement time
- Classification of complaints
- Definition of categories
- QA role
- Complaint sample retention
- FAR
- Trending and review

Sample key insights

- Definition of different types of classes augmented with examples
- Distinction between initial and final classification
- Standardization of process to handle site investigations of ADE
- Detailed complaint trending template

salient features	Lupin	DRL	Torrent	Cipla	Sun	Zydus
log in time	1 working day	NA	NA	1 working day	NA	1 working day
acknoledge time	2 working days of receipt of complaint at site	2 working days	1 working day	1 working day	NA	NA
categorization of market complaint by	site QA	site QA	supply chain management-Export	CQA, DSRM	CQA	Initial assessment and categorization is done by complaint originator in consultation with production head(s). Head QA is the final authority to confirm initial categorization. After concluding investigation, final categorization is to be performed based on the outcome of the investigation.
categorization	critical, major, minor, ADE	medical, quality, chemical	critical (including ADR), major, minor	medical complaint, technical complaint and both	critical, major, minor	critical, major, minor, Non-Substantiated complaint (cannot be categorized in the beginning
critical complaint	significant impact on product quality and/or safety, Product mix-ups, product label issue (such as wrong/missing batch coding details, missing label etc.),	NA	complaints related to product quality / safety / efficacy / regulatory non compliance. Eg. Product Mix Up, Product not meeting regulatory specification, Contamination & Microbial growth, Mix up of printed packaging material, Use of wrong printed packaging material, Wrong labeling, Suspected unexpected serious adverse reactions, Regulatory notices advising recall, Wrong Expiry date, Gross physical change in the product such as discoloration, precipitation. • Failing to meet statutory labeling requirement, content, generic name	NA	Any complaints which are life threatening or can cause serious adverse health consequences to the patient or do not match the designed specification or which may result in a recall, market withdrawal. for e.g. Mix-up, failing specification, microbial growth in sterile products.	Critical Complaints: A complaint related to quality, safety, identity, strength, efficacy, and/or purity of drug product, which may cause irreversible medical situation, potential risk to the patient, or non-compliance with regulatory authorization or critical failure of systems For example, not limited to : • Product Mix-up [for example, product mix up (different strength of same product, different drug product), incorrect label, incorrect lot number/expiration date, unreadable critical data, counterfeit etc.] • Product contamination in case of parenteral products (Particulate matter/extraneous matter) • Microbiological contamination (Sterility / Mold / BET / Microbial count) • Failure to meet the registered specification for distributed product • Metal embedded on drug product • Adverse Drug Events, if considered atypical with respect to the reaction itself (Serious / Unexpected ADE) • Any significant deterioration of the product /Component performance issue

SOURCE: Team discussion

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1 Gold standard SOP includes best practices from all six companies to strengthen the overall complaints management process

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	Receipt of complaint	Categorisation of complaint	Complaint investigation	Complaint closure	Reporting
What's new	▪ Responsibility clearly defined ▪ Standard definitions introduced ▪ Link with PV for ADE related complaints outlined	▪ Complaint classification criteria defined ▪ Standardized definition of complaint categories introduced	▪ Different approaches for carrying out complaint investigation defined (e.g., LOE, ADE related complaints) ▪ Generalized procedure laid out in the form of SOP ▪ Guidance on handling of complaint sample defined	▪ Procedure for closure of complaint laid out (including CAPA finalization, criteria for CAPA extension etc.)	▪ Procedure for tracking of implemented CAPAs for market complaints defined ▪ Approach for review of market complaint trends laid out
Content developed	▪ **Query template** prepared to capture minimum information required from complainant at the time of logging a complaint, by means of standard set of questions	▪ **Category definition** for complaint classification added as annexure	▪ **SOP drafted** on complaint investigation procedure ▪ **Dosage form wise checklists** developed capturing criteria for investigation ▪ Guidance document developed on — Risk assessment tool — Approach to address LOE complaints		

SOURCE: Team discussion

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2

Dosage form wise checklists have been developed to define the investigation criteria for product specific market complaints

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Checklist for market complaint investigation for ophthalmic solution

Type of complaints ⟶	less drops / empty bottle	very hard / difficult to get the drop	Multiple Drops	Drying / precipitation of the Ophthalmic Solution	Black / foreign particle in the bottle	seal attaching to the collar on the neck of bottle was open	over printing missing on label	Bottle not found in carton	Mix-ups
History / repeatability of complaint	√	√	√	√	√	√	√	√	√
Duration of treatment	√	√	√	√	√	√			√
Dispensing date to patient	√	√	√	√	√	√	√	√	√
Date of reporting of complaint to pharmacy	√	√	√	√	√	√	√	√	√
Age of patient/ if the patient self-administering the drug	√		√	√	√				
complaint sample available or not	√	√	√	√	√	√	√	√	√
photograph of complaint sample available or not	√	√	√	√	√	√	√		√
Evaluation of complaint sample/nozzle upon receipt	√	√	√		√				
Simulation performed with complaint bottle			√		√				
appearance of carton	√							√	√
label print condition / smudging of over printed text	√								√
marks on the bottle	√	√	√		√				
if gap is observed between screwed cap and the bottle	√								
BMR review				√	√				
BPR review	√	√	√	√	√	√	√	√	√
challenge test	√		√		√			√	√
AQL checks	√		√		√	√		√	√
review of retention samples	√	√	√	√	√	√		√	
mechanism of getting a drop out of bottle	√	√	√						
Nozzle design / dimensions	√	√	√	√	√				
filling operation review	√		√	√	√				
check weighing operation review	√							√	√
In-process tests review ie. leak test	√		√	√					
In-process tests review ie. visual inspection test	√		√		√	√			
reconciliation of rejections for less weight bottles	√			√	√			√	√
Analysis of the complaint sample upon receipt				√	√				

- **Checklists have been developed for other dosage forms**, like MDIs, PFS, OSD products citing the potential type of complaints that could be received and the respective assessment that needs to be carried out
- **FAQs/query template has been designed** to identify the bare minimum information that needs to be obtained from the complainant at the time of logging the product complaint
- Guidance document has been developed on the approach to address **Lack of Effect (LOE) related market complaints**

SOURCE: Team discussion

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2 Sample of complaint reporting form

Complaint Information			
***Received By:**	Phone Fax E-mail Letter Any other source (Specify)… ……		
***Received on Date**			
***Complainant Type**	Consumer Pharmacist Physician Warehouse C&F Regulatory Sales and Marketing Other (specify) …… Not Available (N/A)	**Response Letter requested by Complainant**	Yes No Not Available (N/A)

Complainant Information		**Additional address details (if required):**
*Salutation:		
*Name (first and last)		
*Company		
*Address:		
*City		

Complaint Description		
Product Information		
1. *Product Description: (where available, include dosage form, strength and pack size)		**8**. *Is product available to be returned? Yes No Unknown
1. Tablet/Capsule marking (imprint)		**9.** *Did the complainant request monetary reimbursement? Yes No Unknown
1. Batch #:		**10.** *Controlled Substances product? Yes No Unknown
1. Expiration Date		
1. Manufacturing Site		**11**. From where the complaint sample will be retrieved from: Patient Pharmacist Wholesaler healthcare facility Other……
1. NDC Number		
1. Sample Storage Condition		
Additional Information (If applicable)		

- **Complaint reporting form to collect the bare minimum information** needed from the complainant at the time of logging the product complaint

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2

Sample checklist for OSD packing related market complaint

Type of complaint	Severity	BMR	BPR	Analytical results of RM/PM/FP	Physical Inspection of complaint / Reserve Sample	Analysis of complaint/ Reserve sample	Check weigher	Stability Data	Method / Process	Wear and tear of Change parts	In-process checks	Procurement of raw material	Calibration / PMP	Complaint log	Qualification	Equipment log book	Operating instructions	Annual Product Quality Review	Incident	Change to procedure	Training
Bitter taste of tablet	Low	√	√	√	√			√	√		√	√		√	√	√		√	√	√	√
Smell defect of product	Medium	√	√	√	√			√	√		√	√		√	√			√	√	√	√
Broken capsule	Medium	√	√	√	√		√	√	√		√	√	√	√	√			√	√	√	√
Black spots on tablet	Medium	√	√	√	√	√		√	√		√	√	√	√	√	√	√	√	√	√	√
Coating peel off	Medium	√	√	√	√	√		√	√	√	√	√	√	√	√		√	√	√	√	√
Product not dissolving	High	√		√	√	√		√	√		√	√		√				√	√	√	√
Difficult to swallow	Low	√			√			√	√		√				√			√	√	√	√
Lack of effect	Medium	√	√	√		√		√	√		√	√			√			√	√	√	√

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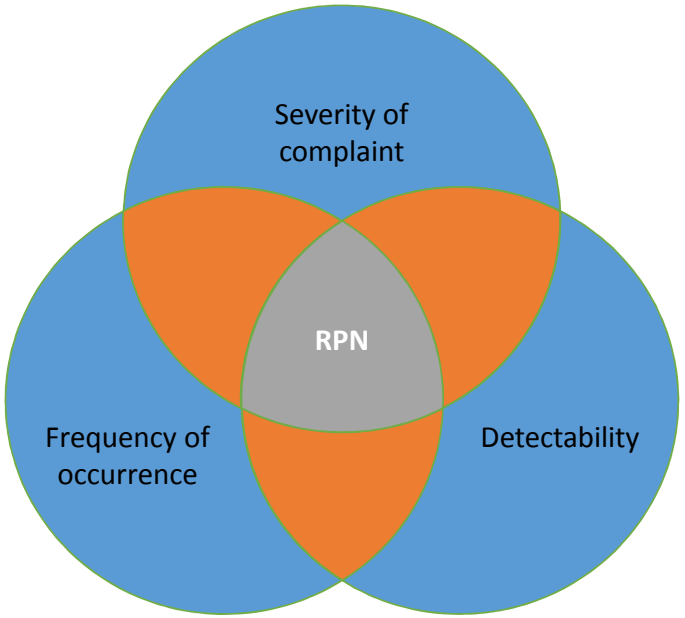
3

Risk assessment approach has been defined to baseline the criteria for raising FAR and/or product recall in response to a market complaint

- If any individual parameter is ≥ 3, it could be a potential case for recall & needs to be evaluated
- If any substantiated complaint has RPN ≥ 6, complaint qualifies for recall decision

RPN Risk Priority Number



Risk scoring methodology

- Based on the concept of assessing severity of the complaint, frequency of occurrence and detectability of defect, to bucket the complaint into a pre-defined category and subsequently evaluate the need for raising FAR/product recall
- Classification criteria (low/medium/high) for "severity of complaint" will be assessed based on the extent of its impact on quality, efficacy and patient safety
- Retrospective review of market complaints will be conducted for identification of repetitive nature and the likelihood of occurrence is ranked depending on frequency of recurrence
- Detectability risk assessed based on the level of detection strength
- **Risk Priority Number (RPN)** = Product of score for severity, detectability and likelihood of occurrence of a given market complaint

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3 Proposed model for end-to-end market complaints management using risk assessment approach

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Prerequisite 1
Complaint data collection template

- Date of complaint receipt
- Product/dosage form
- Complaint type code
- Source of complaint
- Resolution date

Prerequisite 2
Dosage form wise investigation checklist

Receipt of complaint

FAQ/query checklist

Complaint master database maintained by QA

- Record of previous market complaints
- Complaints categorized by product, dosage form & type

Initial complaint classification (based on implication of observed defect on product efficacy & patient safety)

Market complaint investigation using dosage form wise checklists

Complaint categorization into critical/ major/ minor based on investigation

Risk assessment to evaluate need for initiating FAR and/or product recall

Master data base updation based on complaint investigation outcome and closure date

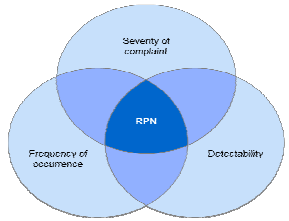
Critical

Non-critical

Evaluate need to raise FAR

Market complaint categorization based on severity, frequency of occurrence and detectability

Risk assessment model



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