World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

Check for updates

Prioritizing metal detector for finished pharmaceutical formulation: Manufacturing safe, quality product

Ishita Sharma [1,*], Kumud Upadhyay [2] and Sushil Giri [1]

[1] *Department of Pharmaceutics, MIT College of Pharmacy, MIT Group of Institutions, Moradabad-244001, Uttar Pradesh, India.*
[2] *Department of Pharmaceutical Sciences, Kumaun University, Nanital-263136, Uttara Khand, India.*

World Journal of Advanced Research and Reviews, 2022, 16(03), 482–489

Publication history: Received on 01 November 2022; revised on 12 December 2022; accepted on 14 December 2022

Article DOI: https://doi.org/10.30574/wjarr.2022.16.3.1339

Abstract

Background: The pharmaceutical metal detector is a device to detect metal as well as non-metal contaminants of large size in the pharmaceutical dosage form. The detection of unwanted metal (contaminant) is important to produce a high quality of the dosage form.

Main body: Pharmaceutical dosage forms are highly sensitive to the environment to which they are surrounded. It is challenging to keep a product in its original form throughout its shelf life. These metals find entry in the pharmaceutical formulation during various phases of manufacturing while passing through pipelines, sieves, conveyors, wires, buds, error in mixing processes, through raw materials. The Food and Drug Administration Hazard Evaluation board has given that the length of 0.3 inches to 1 inch of metal is considered unacceptable. The article highlights source of the metal contamination in pharmaceutical formulation types of detectors used, FDA standard for the metal detector, the need for a metal detector with its ideal properties, effect, hazards of ingesting metal fragments through medicines, working principle, uses, separation of metal contamination, test for the metal detector go about when metal is detected. Monitoring of system in a metal detector at the Critical control points some case studies involve reputed pharmaceutical manufacturers, which were forced to recall the batches for metal fragments detected in finished product.

Conclusion: The pharmaceutical companies are bounded to produce quality safe products. One adulteration may cause recalls of products, cost loss of millions of dollar or total disruption of business as well. The selection of suitable metal detector is much needed. As the metal detector inclusively controls the contamination maintains a tough control on the quality of products.

Keywords: Metal detector; Metal contamination; Quality; Safety; Hazards; Ferrous non-ferrous; Recall

1. Introduction

Metal detector is a device, used to detect traces of magnetic or conductive metal present in pharmaceutical formulation. In pharmaceutical preparations there are many metals that are categorized as useful metals. These include Sodium, Potassium, and Magnesium. Sodium and potassium are alkali metals that occur in body that play role in homeostasis. Magnesium is alkali earth metal found in bones, soft tissue, skeletal muscles and plays important role in some metabolic signaling pathway [1]. Every metal is toxic in high concentration. On the other hand, the term heavy metal refers to metallic elements that have a relatively high density and are toxic or poisonous at low concentrations. Examples of heavy metals include mercury (Hg), cadmium (Cd), arsenic (As), chromium (Cr), thallium (Tl), and lead (Pb) [2].

* Corresponding author: Ishita Sharma

The occurrence of unwanted metal where it is not needed is considered contamination. FDA (Food and Drug Administration) demands testing of finished product by metal detectors for consumer's safety. Metals as contamination are important to detect with high accuracy and reliability. This is significant to ensure product safety. As per GMP (Good Manufacturing Practices) standards the final food pharmaceutical products must always be free from metal contaminations. Mostly the metal detectors are used by the US State Department of Agriculture (USDA), US Food Drug Administration (USFDA), Hazard Analysis Critical Control Point (HACCP) Certifications in India, other countries [3]. HACCP is a management system in which food safety is addressed through the analysis and control of biological, chemical, and physical hazards from raw material production, procurement and handling, to manufacturing, distribution and consumption of the finished product [4].

Metal contamination can be found in food products or pharmaceutical products due to the presence of metallic components (like- pins, wires, buds, punches, eroded or co-eroded metallic parts, etc.) as stainless steel, ferrous or non-ferrous materials. Deducting these metal components is very important.

Figure 1 Metal particle in a compressed tablet [5]

2. Metal detecting process

The metal detecting process should be highly accurate reliable. Thus, metal detectors play a crucial role in finding such contamination in pharmaceutical products. Moreover, metal detectors are ideal products for maintaining an organization or company reputation.

2.1. Source of metal contamination in pharmaceutical formulation

There are several possibilities of various contaminations in the pharmaceutical industry. Contamination is unwanted material in the final product. The classifications of contaminants in pharmaceuticals are biological contamination, pyrogenic contamination, chemical Contamination and physical Contamination [6]. Among these contaminations, metal falls under the category of physical contamination. Physical contaminants enter through the manufacturing and packing process. These processes use metal and non-metal equipment. So, the chances of contaminant being present in pharmaceutical formulation are high. The possible source of metal may enter in formulation with raw material, mixing process error, machine failure during manufacturing/packing operations.

Table 1 The sources of Metal Contaminations [7]

S. No.	Source of Impurity	Impurities
1.	Machinery	Machine that are aged, two metals parts rubbing continuously, parts that are not properly tightened or fixed
2.	Raw Ingredients	Chips and flakes of metal through pipeline, tanks bins
3.	People	Intentional accidental
4.	Environment	HVAC failure, building failure

2.2. Types of a metal detector

Over the years Pharma industry has prepared itself to the challenge posed by these metal contaminations. It has developed several means to detect metals in finished products [3]. Depending on the type of contamination a detector can be of different type. There are various types of detectors used to detect metals in the formulation or finished product. Based on different parameters the detectors are classified as-

2.2.1. Based on types of contamination:

- Ferrous metal detector
- Non-ferrous metal detector
- Stainless steel detector

2.2.2. Based on type of formulation:

- Metal detector for Solids, example for Tablet Capsule
- Metal detectors for Liquid preparation, example for Suspension, Paste

2.2.3. Miscellaneous:

Advance metal detector: X-ray detector etc. [8].

The Metal contaminants are categories in three forms: ferrous, non-ferrous and stainless steel. The ferrous contaminations such as chrome steel are both magnetic and are good electrical conductor that is why they can be detected easily. Non-ferrous metals contaminants are non-magnetic generally excellent conductors and are relatively easy to detect. Metals such as Aluminum, Brass, Lead, and Copper fall under Non-ferrous metal contaminants. Stainless steel comes in different grades is usually non-magnetic, electrically poor conductor. Thus, they are difficult to detect by ordinary means. The overall capability of the metal detector is the sensitivity ratio between ferrous and the most complicated is to spot ranking of stainless steel [9]. Based on the type of formulation solid metal detector is used for oral solid dosages like tablets, capsules while liquid metal detectors are used for solutions, suspensions, paste. The advance metal detector includes an X-ray metal detector. It is an advanced type of metal detector. X-ray metal detector detects not only metals but also plastic, glass other contaminants also verify package integrity dosing portions. Criteria for selecting metal detectors must be based on the following points but will not be limited to these only. The key aspect is the Sensitivity of the metal detector. Sensitivity is explained as the smallest sphere of a particular metal or non-metal that the unit can detect as it passes through the metal detector. A metal detector used in pharmaceutical industries are available in different sensitivity *e.g.,*0.15mm diameter ferrous, 0.2mm diameter non-ferrous and 0.3mm diameter for stainless steel particles. The industries require sensitivity at the time of the "Qualification of Equipment" to be considered as priority parameter. Quantification of equipment is initial verification of quality of instruments to fulfill the specific need at the time of procurement. The Sensitivity of Metal can be affected by many factors such as type of metal contamination shape of metal contamination [10]. Secondly, Metal detector capacity is usually denoted by tablet/minutes. Thirdly, the accessibility to store data in metal detector (*e.g.,*100 product materials), the last availability of auto validation option or any other requirement as per firm.

2.3. FDA standards for Metal detector metal detector with ideal properties

The FDA's Health Hazard Evaluation Board provides limit of metals fragments that are unacceptable in formulations. Any metal impurity beyond 0.3 inch to 1 inch (7mm to 25mm) is considered unacceptable. Any foreign material found in the formulation is considered unsafe or adulterated [11, 12].

In manufacturing units of tablets or capsules, there may be the chance of metal impurity either ferrous, non-ferrous, or tramp metals. The presence of metal in dosage form impacts the quality of product as the metal piece may initiate any other reaction, also their presence may damage other equipment and also is hazardous for the consumer. To overcome such challenges metal detectors are frequently used. These metal detectors are designed to detect metal impurities without disturbing the routine manufacturing process. For effective detection a metal detector must be designed to ensure metal free product in cost effective manner. To serve this purpose the metal detector used in the pharmaceutical industry must have few basic properties. It should be simple to use, reliable, sensitive, capable to detect magnetic non-magnetic metal, compatible with other machines like compression machines in case of OSD (Oral Solid Dosage form), efficient for online metal detection rejection. It should occupy minimum space as possible, easy to clean most importantly it should record the date and time of operation [13].

2.4. Effects Hazards of ingesting metal fragments through medicine

The Hazards of ingesting metal may depend on the shape and size of the metal that was ingested. The smooth edges or small parts of metal being ingested will probably be fine [14]. Metals like Iron, Copper, Aluminum, Nickel, and others of the same nature are not harmful unless they have sharp edges that can cut the esophagus. Metals with smooth or small edges will simply pass-through GIT (Gastrointestinal tract) leave the body with usual waste. On the other hand, if someone ingests sharp edges or harmful metal through any medicines, it can potentially be life-threatening. As it depends on the metal, if the metal is highly radioactive or toxic it can easily be hazardous or even fatal [15]. The effect of accidental metal ingestion in human is that they may feel inability or painful swallowing, vomiting, drooling, also sometimes chest pain neck pain. In this case, one should not panic do not try to vomit as it may cause injury [14].

2.5. Working Principle of Metal detectors

Different metal detectors work by different possible mechanism which can be-

- Balance coil metal detector
- Magnetic field metal detector
- Pulse inductive metal detector

2.5.1. Balance coil metal detector

It is based on the balance between the three interconnected coils. As the current flow, they work as a transmitter which generates a field that acts as a radio transmitter. The second coil receives it the third coil is connected to the detector. If metal comes in the field generated by the first coil; it is detected by the second third coil. The detector detects the particle due to the conductive or magnetic property of the metal. e*.g.,* PH1030 Pharma Metal detector.

2.5.2. Magnetic field metal detector

When a magnetic particle passes through the detector, a current is generated this is amplified thus detects the metal particle. Another approach is when a conductive material is present in a magnetic field or formulation is conductive in nature then it generates signals if non-magnetic metal passes. However large pieces of non-ferrous metals stainless steel are detected. This is useful for detecting non-ferrous metals in drugs medicines.

2.5.3. Pulse inductive metal detector

Its principle is based on electromagnetic induction. It is used to detect ferrous as well as non-ferrous metals. It is insensitive to very small metal-like foils which have thin low conductive power. Whereas it is sensitive to some bigger materials. This type of detector uses more coils working together which sent a short powerful current through the coil that generates the magnetic field. When this pulse ends it generates a sharp electrical spike. A Pulse induction-based metal detector sends 100-120 pulse per second but the number may vary based on the manufacturer model. e*.g.,* Vinsyst Pulse Induction Metal Detector [3].

2.6. Uses of metal detector

The metal detector works by attaching it after any operational process. In the process, if the metal is revealed the magnetic field changes the detector works by opening the rejection flap by pneumatic valve. The contaminant is rapidly rejected with little loss of material. After completing the process, parts of the detector are dismantled for cleaning product change over. Combined with all types of the tablet press deducting unit [16].

In liquids, metal detection is done prior to the capper induction sealer. This is because most metal detectors are unable to perform the inspection after foil seal adheres to the bottle. Therefore, the inspection in liquids performed without cap on the bottles to increases the possibility of metal as well as other contaminants entering the bottle accidently during the inspection. The recent advancement in the technology permits an inspection with foil seal to be tested after the induction sealer. Hence the process will make the product a complete metal-free product. The contaminants detection is always affected by bottle size, foil thickness, and foil position [7].

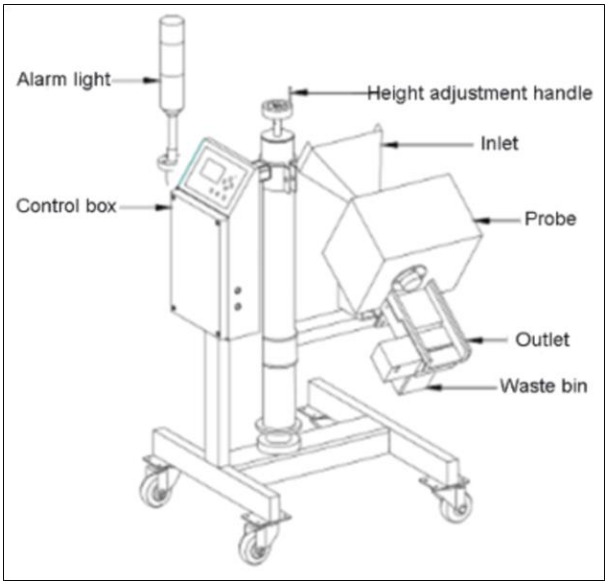

Figure 2 Pharmaceutical Metal detector

2.7. Separation of metal contamination

The separation process is an integral part of the metal detector but independent mechanical solutions are not uncommon. There are two ways of separating metals processes: The first one is with manual sorting of contaminations if metals are detected, the detector rings alarm message belt stop. But the drawback of this process is that operator may act incorrectly or human error may occur. To overcome this effect second type of separation system is available which separates the metal contamination by automatic separation mechanism. These are Pulse blow out ejector, pusher, telescopic conveyors, and separation mechanism in the free fall application [18].

2.8. Test for the metal detector goabout's when metal is detected in the medicines

Pharmaceutical Industry must make sure that equipment working accurately in different time interval, which is referred to as verification. To follow this rule the Metal Detector should be tested to know whether it is working in agreed sensitivity or not. In this test, metal balls of fixed diameter are encapsulated in non-metallic or plastic blocks passed through the metal detector. These metal balls are ideally made with Ferrous (FE), Non-Ferrous (NFE), and Stainless Steel (SS) [19]. If metal pieces are detected then pre-established corrective action procedures are followed which should be firstly to hold on to the product or destroy the batch. Production should not begin without an operating metal detector, to try avoiding the source of metal fragment, to ensure maintenance of metal detector in a regular period so that its sensitivity remains accurate [11].

Figure 3 certified metals for verification of metal detector

2.9. Monitoring of system in a metal detector at the critical control points (CCP)

The CCP is key variables affecting the pharmaceutical production process. The operational conditions within this range are considered acceptable for operation as standards. Any deviation from this acceptable range will be indicative of issues within the process. As critical control point of metal detector must be monitored frequently. These are monitored for various purposes such as for internal error monitoring, audit trail, and user management. The internal error monitoring program should be done by carry out an internal error search error analysis. The second one is Audit Trail that shows us the record about who assessed the system with Date and Time. The Error messages warnings are also recorded logged. If in case settings that influence the sensitivity of metal detector changes, it should be recorded in the audit trail when carried out. The third one is the User management system that should also be monitored. Access authorization should be designed according to system relevance. If any unauthorized person confirmed, a warning message without restoring production safety in the CCP, then CCP should not be valid [20].

2.10. Some cases of metal contamination reported from the Industry

Table below lists some cases of manufacturers forced to recall of product from the market due to metal impurities product causing embarrassment to some pharmaceutical companies. The detail of recall is discussed as case studies following the table of recall.

Table 2 Product recall by Pharmaceutical Manufacturers

S. No.	Company	Recalled Product/Year
1	Lupin Pharmaceutical Inc.	Cefdinir oral suspension 2019
2	Johnson and Johnson	Rolaids Antacid 2010
3	Johnson and Johnson (McNeil consumer healthcare)	Tylenol2009
4	Johnson and Johnson -Merck Consumer Pharmaceuticals	Infants' Mylicon gas relief dye-free drop nonstaining 2008
5	L. Perrigo Company	Acetaminophen 500mg caplet 2006

2.10.1. Case study 1

In 2019, Lupin Pharmaceutical Inc. was forced to recall over 18000 bottles of oral suspension, Cefdinir used for the treatment of broad range bacterial infection. The batch was manufactured in Lupin's Mundideep manufacturing facility, Maryl. The enforcement report of United State Food and Drug Administration (USFDA) stated that metal piece was identified in the product. The USFDA categories the recall falls under Class-II recall. Class II recall referring to the use of a violative product that may cause reversible loss bare possibility of serious adverse effects [21, 22].

2.10.2. Case study 2

In 2010, Johnson and Johnson announced a national recall of more than 13 million packages of Product Rolaids, an antacid drug. These drugs were detected with metal wood particles. The firm said these particles were introduced in the formulation during third-party manufacturing [23, 24].

2.10.3. Case study 3

In 2009, black specks are found in bottles of product infant's Tylenol. FDA began to investigate the consumer's complaints discovered that the specks were metal pieces including nickel, iron and chromium. The product was manufactured in Johnson and Johnson subsidiary, McNeil consumer healthcare's plant in Fort Washington. After this metal detection, the plant continued the production of Tylenol for several months. While they also recalled that batch but a follow-up investigation by FDA revealed that the firm had failed to show corrective action plans. After 5 years of further investigation, FDA levied a $25 million criminal fine against McNeil Healthcare [25].

2.10.4. Case study 4

In 2008, Johnson and Johnson- Merck Consumer Pharmaceuticals Company announced a nationwide recall of the product Infants' Mylicon gas relief dye-free drop nonstaining. This was due to the presence of metal fragments in the product. [23, 26].

2.10.5. Case study 5

In 2006, L. Perrigo Company informed FDA that metal contamination was found in Acetaminophen 500mg caplet they decided to recall all products produced by that firm. The GMP-related inspection was planned in that firm. During the investigation of many days, the external investigating unit ruled out the manufacturing process as the cause of metal fragments finding. The other reason sighted was due to raw material. So metal fragment were photographed matched for similarity. In the second inspection, they rechecked the batch found metal fragments throughout the batch. The entire batch was rechecked additional rejected metal was observed. As a result of Medical Risk Assessment Evaluation, large wire fragments are a potential threat if ingested, thus recalling of the product became necessary. During inspection of the firm, the external investigation team reviewed the Metal Detector equipment Log Book record for the previous two years. During these 5 more cases of previous metal detection were found. In the preventive action, the firm installed Metal Detector made a protocol for checking raw material. By this, they made sure that the metal fragment were detected removed. They also designed the sampling protocol to collect samples from each drum also follow the first in first out system. (Stabilishment injection report L.Perigo Company).

3. Conclusion

The Global Market of Pharmaceutical Metal Detector is expected to be $1.6 billion by 2022 will grow exponentially. As the metal detector inclusively controls the contamination maintains a tough control on the quality of products. It is widely accepted by various regulatory authorities their use should be mandatory for Pharmaceutical Industry. The pharmaceutical companies are bounded to produce quality safe products. One adulteration may cause recalls of products, cost loss of millions of dollar or total disruption of business as well. The selection of suitable metal detector may be hit trial process that should consider ease of use or operation, sensitivity most important audit ability. At the same time, using a metal detector is not fully assured that the formulation is free from any metal pieces. In future, advance metal detector, best metal detectors and reviews over top 5 metal detectors can be the good headings to cover as these are unexplored areas.

Compliance with ethical standards

Acknowledgments

The authors are thankful to MIT College of Pharmacy, Moradabad, Utter Pradesh, and India for providing the necessary facilities to accomplish the work.

Disclosure of conflict of interest

The authors declare no conflict of interests.

References

[1] Chellan. P andSadher P.J.(2015), " The elements of life and medicine", Phil. Trans. The royal society publishing, 373:20140182.http://dx.doi.org/10.1098/rsta.2014.0182

[2] Singh. R and et al., (2011), "Heavy metals and living system: an overview", Indian Journal of pharmacology, volume 43(3), page no.246-253

[3] Mal. D, Metal detector: Types uses in pharmaceutical industry, http://www.pharmabiz.com/ArticleDetails.aspx?aid=75768andsid=21#:~:text=Metal%20detectors%20are%20used%20in,or%20corroded%20metallic%20parts%20etc. Published date 06.06.2013 , Pharmabiz.com, Accessed on28.02.2021

[4] https://www.fda.gov/food/guidance-regulation-food-and-dietary-supplements/hazard-analysis-critical-control-point-haccp accessed 19.1.2022

[5] Stellmack. M, Rhodes. K (2010), Metal contamination in Bio-pharmaceutical drugs, https://www.contractpharma.com/issues/2010-10/view_features/metal-contamination-in-bio-pharmaceutical-drugs/ Published date 10.08.10, Contract pharma, Accessed on28.02.21

[6] Pharmaceutical contamination: Types, causes prevention https://lindstromgroup.com/in/article/pharmaceutical-contamination-types-causes--prevention/ Published date 27.08.2020 Lindstrom group, Accessed on14.02.2021

[7] Zarnick. K, "Helping keep pharmaceuticals safe: metal detection overview guidelines", White Paper PI.0101, Thermo scientific, Page no. 1-4.

[8] Thomas. P, Testing your metal: Best Practice from PTI https://www.pharmamanufacturing.com/articles/2010/058/ Published on 12.04.2010, Pharma manufacturing, Accessed on27.04.2021

[9] "Safeline Metal Detection and X-ray inspection" Mettler Toledo, "Detecting more metal for increased br protection" Page no. 1-4.

[10] Raju. A, Metal detectors hold the key for safety in Pharma sector http://pharmabiz.com/ArticleDetails.aspx?aid=115585andsid=21 Published date 14.02.2019, Pharmabiz.com, Accessed on23.04.2021

[11] https://www.fda.gov/media/80342/download, Accessed on14.02.21

[12] Bowling. S, FDA metal detection Stards, https://t2conline.com/fda-metal-detection-stards/Published on 23.10.2017, Time square chronicles, Accessed on14.02.2021

[13] Abernethy D.R et al.,(2010), "Metal Impurities in Food and Drugs", Pharmaceutical Reserch, Volume 23, 750-755.

[14] Frane. J, What happen if I swallow a very small piece of metal?,https://www.quora.com/What-happens-if-I-swallow-a-very-small-piece-of-metal Answered on 12.04.2019, Accessed on28.02.2021

[15] Reese.C.A, What happen if I swallow a very small piece of metal?, https://www.quora.com/What-happens-if-I-swallow-a-very-small-piece-of-metal Answered on 12.02.2019, Accessed on28.02.2021

[16] Tablet Metal detector https://www.prismpharmamachinery.com/metal-detactor.html, Prism Pharma machinery, Accessed on14.02.2021

[17] "Requirement, Technology application recommendations Metal Detection in production lines", https://www.geass.com/wp-content/uploads/filebase/minebea-intec/metal_detector/Rilievo-dei-metalli-nelle-linee-di-produzione-Minebea-Intec_en.pdfSartorius Intec- A minebea group company, page no. 1-32

[18] "Requirement, Technology application recommendations Metal Detection in production lines", https://www.geass.com/wp-content/uploads/filebase/minebea-intec/metal_detector/Rilievo-dei-metalli-nelle-linee-di-produzione-Minebea-Intec_en.pdfSartorius Intec- A minebea group company, page no. 1-32

[19] How to test a metal detector https://www.pharmaceuticalonline.com/doc/how-to-test-a-metal-detector-0001, Accessed on02.03.2021

[20] "Requirement, Technology application recommendations Metal Detection in production lines", https://www.geass.com/wp-content/uploads/filebase/minebea-intec/metal_detector/Rilievo-dei-metalli-nelle-linee-di-produzione-Minebea-Intec_en.pdfSartorius Intec- A minebea group company, page no. 1-32

[21] Lupin recall over 18,000 bottles of antibiotic drug in US https://www.thehindubusinessline.com/companies/lupin-recalls-over-18000-bottles-of-antibiotic-drug-in-us/article27955724.ece/amp/ Published on 16.06.2019,The hindu Business line, Accessed on25.04.2021

[22] Lupin recalls over 18000 bottles of antibiotics drug in the US https://www.livemint.com/companies/news/lupin-recalls-over-18-000-bottles-of-antibiotic-drug-in-the-us-1560662580896.html, Published on 16.06.2019, Mint ePaper, Accessed on25.04.2021

[23] Patel. R.B, Patel M.R, Patel.B.G, Detection of metal contamination: an overview, http://www.pharmabiz.com/PrintArticle.aspx?aid=63358andsid=0 Published on 09.06.2011, Pharmabiz.com, Accessed on 25.02.21

[24] Singer. N, J. andJ.Unit issue recall of Rolaids, https://www.nytimes.com/2010/12/10/business/10recall.html#:~:text=A%20unit%20of%20Johnson%20%26%20Johnson,wood%20particles%20in%20the%20products published on 09.12.2010, the new work time, business, Accessed on26.02.21

[25] Tylenol contamination the drug recall epidemic, https://www.elementum.com/chain-reaction/tylenol-contamination--the-drug-recall-epidemic published on 23.03.2015, Elementum, Accessed on26.02.2021

[26] Drucker. R, Voluntary recall: Infants' Mylicon Gas Relief Dye Free Nonstaining Drops, https://www.jwatch.org/pa200811190000001/2008/11/19/voluntary-recall-infants-mylicon-gas-relief-dye, published on 19.11.2008, NEJM Journal watch, Accessed on26.02.2021

[27] Stabilishment injection report L.Perigo Company, Allegan, MI. 49010, FEI 1811666, EI start 11/Nov/2006 EI end 12/Dec/2006, Page no. 1- 84