

*Development of risk
assessment and decision
support tool for
pharmaceutical*

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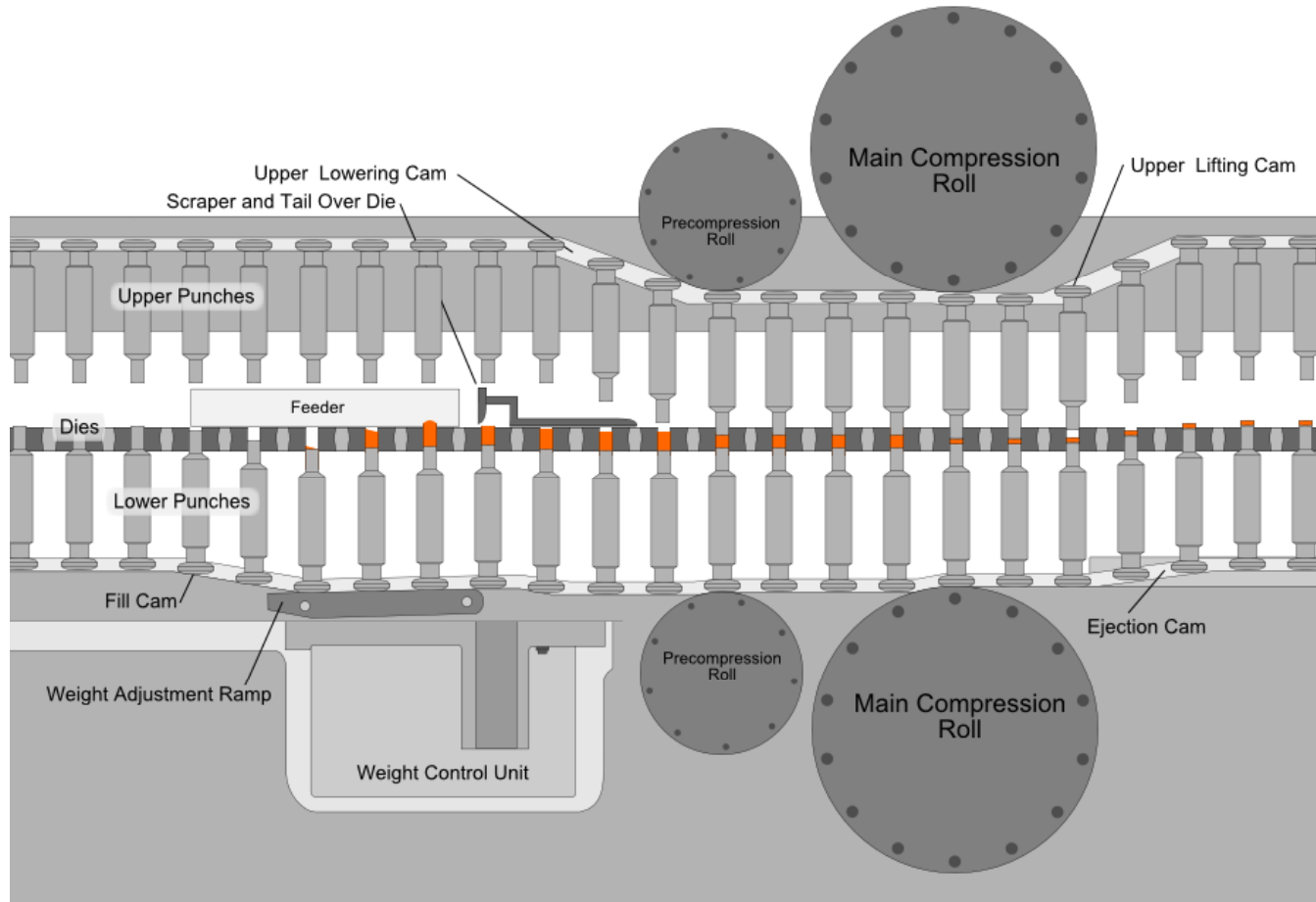
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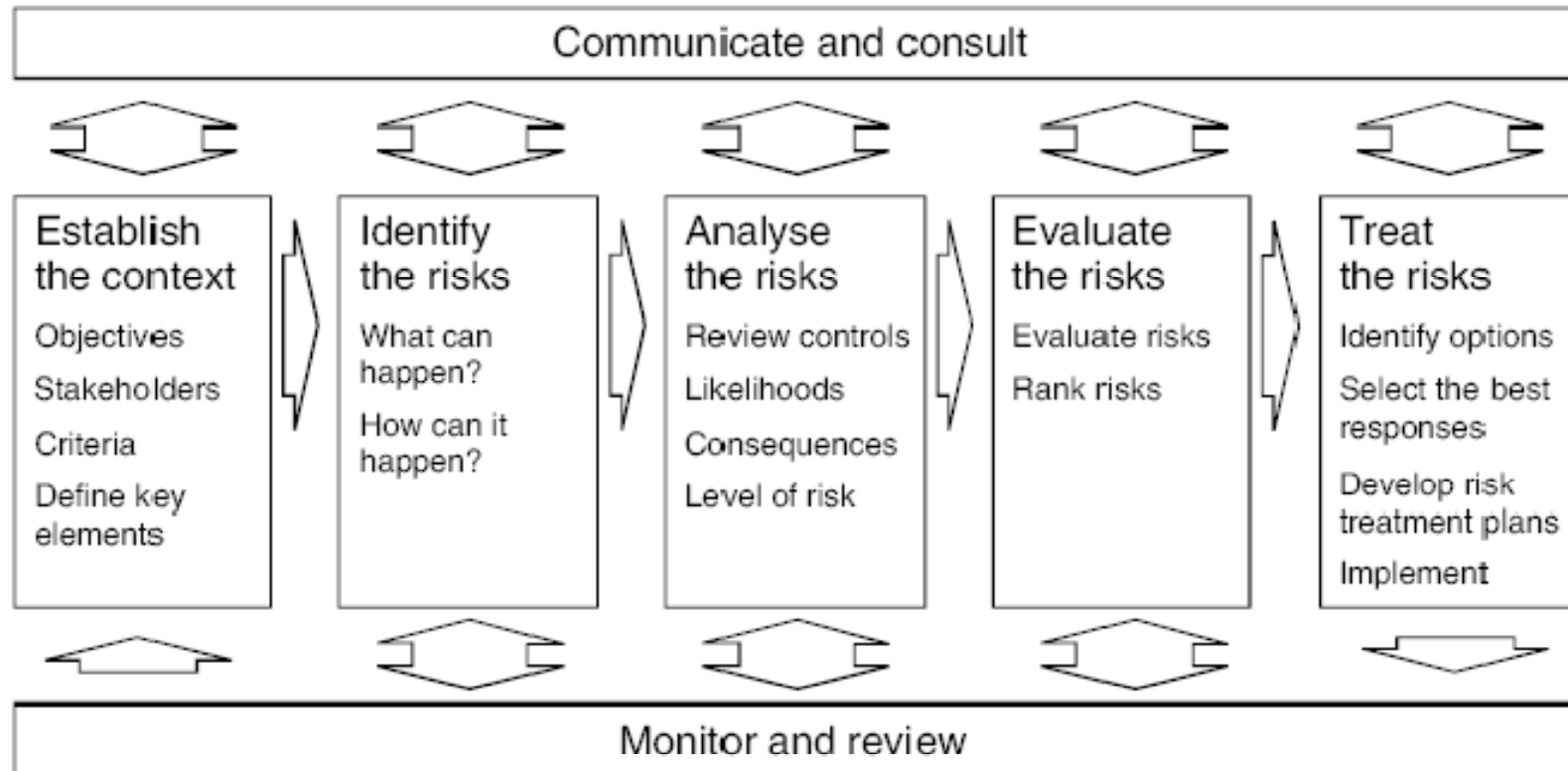
Overview

- Medicine rejection
 - Quality assurance
 - Recalls
 - rejections
- *Compression*
 - Binder
 - machine
- *Quality Parameters*
- Hardness, Moisture, D time and friability
- Risks
- Risk management
- Decision support systems
- Bayesian Networks

Tablet Manufacturing

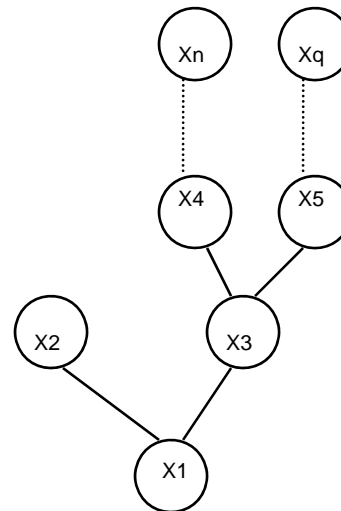


Risk Management



Risk assessment Decision support tools

- Statistical / mathematical tools
- Simulation based tools
- Software
- Probability of event
- Bayesian Networks





Case Study

- Charewel Pharmaceutical
- Micro Crystalline Cellulose , Avicell
- Avicel
- Vivapur
- Accell
- Reports
- Labor costs and risks
- Knowledge Gap
 - Hazard Identification
 - Abnormal Event management in Pharmaceutical Production

Analytical Parameters (MCC)

S.#	Test	Specification	AVICEL; FMC Germany	VIVAPUR; JWS Germany	ACCELL; ACCENT MICRO CELL India.	Remarks
1	Physical form	granular powder	More coarse form.	more fine form	more fine form	Q/C PASSED
2	Color	white	complies	complies	complies	---do---
3	Solubility	Insoluble in water, acetone.	complies	complies	complies	---do---
4	Loss on drying	Not more than 7%	3.5%	5.0%	6.8%	---do---
5	Identification	Turn to violet with iodinated ZnCl ₂ solution.	complies	complies	complies	---do---
6	pH	5—7.5	6	6.8	7.5	---do---
7	Bulk Density	0.28—0.33 g/ ml	0.33	0.29	0.29	---do---
8	Particle Size retained on airjet sieve.	(60 mesh) max 8% (200 mesh) min 45% [^]	< 2% 60 %	<3% 57 %	< 5% 46 %	---do---7

Physical Parameters

S.	Source. #	Weight mg	Diameter. mm	Thickness mm	Hardness kg /cm ²	Friability NMT 1%	Reference
1	AVICE L.	120 \pm 7.5%.	7.1	3.1	8	0.1	<p>Coating; A stable product (cores) produced that is resistant to extreme shearing forces produced when CORES are charged to conventional coating pan.</p> <p>Speed, 10 rpm</p> <p>Charge weight; 12 kg</p> <p>Air gun pressure;100psi</p> <p>Gun distance; 50 cm from flowing bed.</p> <p>Coating solution; 10 liters of solution applied in sequence of 500 ml / gun. (20 guns).</p> <p>Blister; ALU, ALU pneumatic pressure blister machine is being used with 7.5 mm sized impression punches, producing 4 mm deep bubbles with 1% variation at speed of 10 strokes / minute.</p>
2	VIVAP UR	120 \pm 7.5%.	7.1	3.8	3.5—4	0.7	
3	ACCEL L.	120 \pm 7.5%.		3.1	2.5---3	1.2	

In Process Report

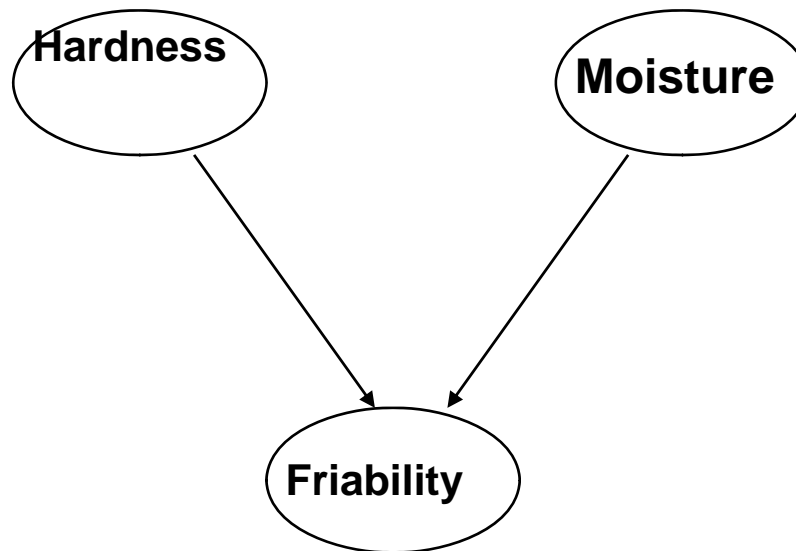
S.#	Brand name	Source.	Behavior 1.	Rectifications. 1	Behaviour.2	Rectifications. 2
1	AVICEL.	FMC Germany	<i>Complies ;</i> Coating is acceptable Tablets are easy to fit in blister strip pocket.	NA	NA	NA
2	VIVAPUR	JWS Germany	<i>Complies;</i> Coating is acceptable Tablets are easy to fit in blister strip pocket.	NA	NA	NA
3	.Accell	ACCENT MICR OCEL L India	<i>Not Complies;</i> During application of 5 th gun, the upper surface of the cores show shredding and the coating film was not produced, even on addition of film former by 30 %. <u>Result;</u> Quality assurance ceased the process and a rectification was advised by quality control deptt. So the process was stopped for rectification.	A hardness of 6 kg /cm was achieved by following process. Weight; 150 mg.± 7.5%. Thickness; 3.8mm Diameter; 7.1mm Addition; 30 mg of MCC per tablet.	Product showed a stable behavior in coating pan. When blistering, 2 out of ten tablets showed sticking with covering aluminum foil. result; Quality assurance ceased the process and a rectification was advised by quality control deptt. So the process was stopped for rectification	A new purchase order generated to arrange AL_AL foil 300micron That formed bubble depth of 5mm with 1% variation at speed of 10 strokes / minute.

Rejection /reprocess report

Avicel FMC (GERMANY)		
Day 1st		
08 man hrs of team comprising 07 officers and 06 workers. Chemical/process expenses.@ RS 5000 per sampling. Power/ utilities expenses @ Rs 10,000 per working day.		
PROCESSES;		Status
1	Formulation	ok
2	Requisition order for Raw materials Packing materials.	ok
		ok
		ok
3	Dispensing of materials .	ok
4	Issuance of materials.	ok
5	Blending of materials	ok
6	Q/A SAMPLING	ok
7	Q/C RELEASE	ok
8	Compression oftablets(Cores)	ok
9	Q/A Inprocess checks.	ok
10	Q/C RELEASE for coating	ok
11	Coating solution preparation	ok
12	Tablet coating.	ok
Day 2nd		
08 man hrs of team comprising~ officers and 20 workers. Chemical/process expenses.@ RS 5000 per <u>sampIIng</u> . Power/ utilities expenses @ Rs 10,000 per working day.		
PROCESES;	Blister and packing.	ok

Proposed model

- Hardness
- Moisture
- Friability



Bayesian Process

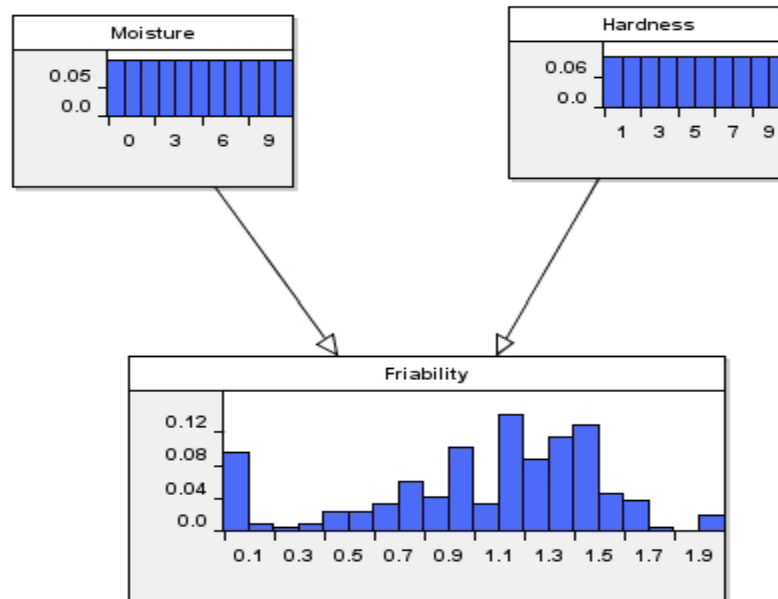
Hardness	High	0.95	Hardness	High	Low	Good	0.7	Moisture
	Low	0.05	Moisture	Good	Poor	Good	Poor	
			Friability	Probabilities				
			Acceptable	0.95	0.7	0.7	0.01	
			Rejected	0.05	0.3	0.3	0.99	

Friability

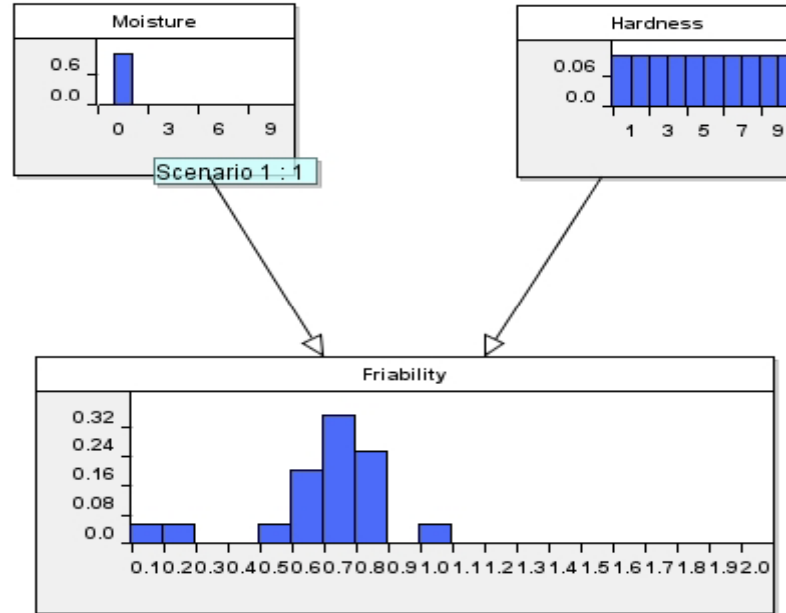
1. Initial Probability of an event
2. Calculation of probability on risk value
3. Difficult for human, software is used

$$P(A / B) = \frac{P(B / A) \cdot P(A)}{P(B)}$$

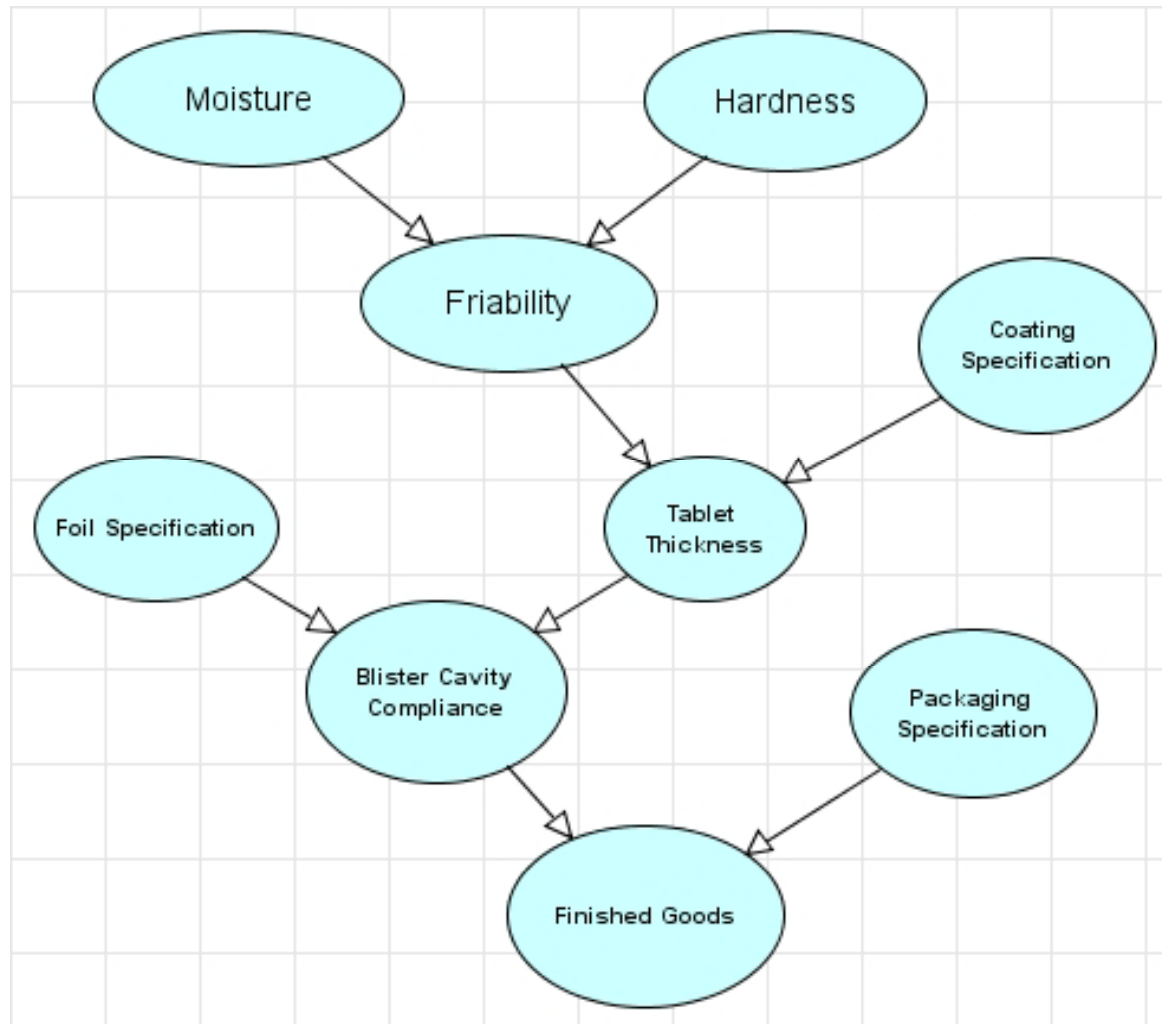
Proposed solution



Execution



Further Extension of Model





Conclusion

- Risks in tablets manufacturing can be fatal
- Risks can be minimized by pre assessing their reasons
- Using the proposed model we can analyze the possibility chain event occurrence and plan to avoid or manage them



References

- “Pharmaceutical Informatics is a novel Paradigm” [Zhao, 2005]
- “There exist a strong need of informatics in pharmaceutical product development” [Zhao, 2005]
- “Tools are required in Information management and decision making” [Zhao, 2006]
- “It is required that model development in specific domains of pharma is carried out” [Zhao, 2006]
- Computers in Pharmaceuticals (research exemplary book) [S. Ekins 2006]
- Use of statistical methods in pharma.
- “The use of Bayesian Theory is increasing in recent times” [Spiegel DJ 2000]