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The Design and Qualification process for a LVP packaging system from a user perspective case study: Nitrosamines

Rawaa AMMAR

24 Mar 2021

Outline

LVP design requirements

E&L strategy

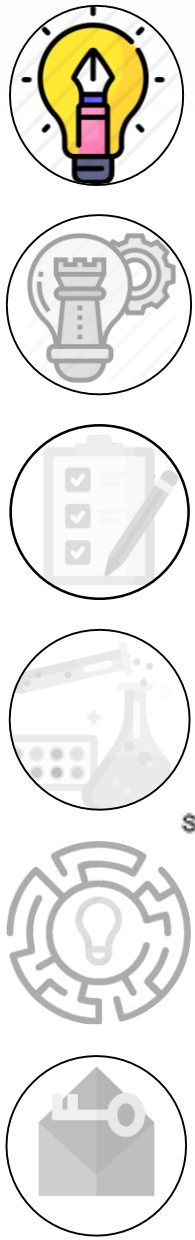
E&L supporting data

LVP: E&L study design

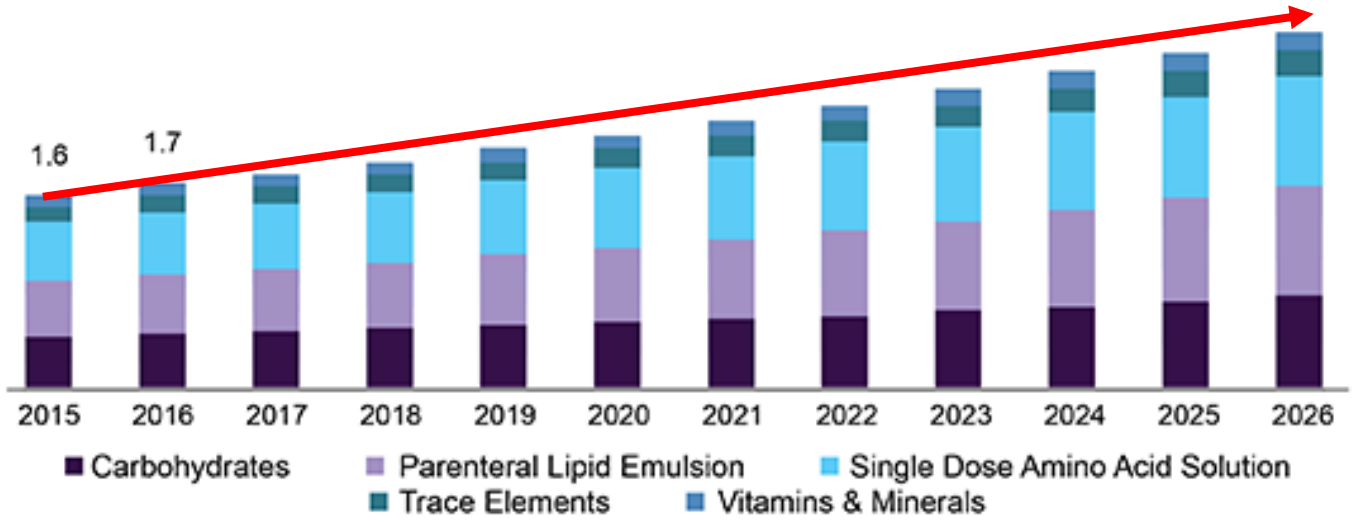
Challenging case study: Nitrosamines

Key takeaways

Patient needs drive LVP development



US PN market size 2015-2026 ($B)



Source: www.grandviewresearch.com

- Various drug formulations/chemistry
- Sophisticated packaging system
- Diverse packaging formats
- Different populations of patients
- Several dosing regimens
- Multiple durations of treatment

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LVP design requirements

Primary packaging

Transparency

Even sealing properties

Even peelable properties

Light protection

Sterilization resistance

Pharmacopoeia compliant

Chemical compatibility

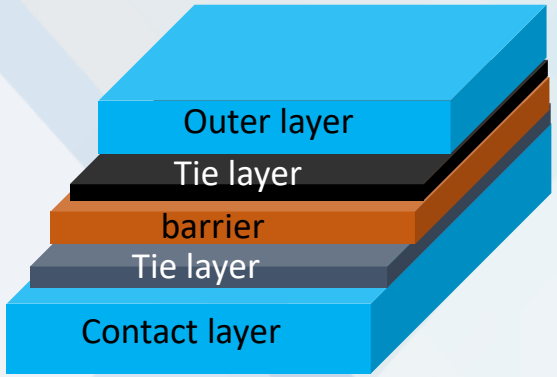
Low migration

Flexibility

O_2 O_2

O_2 barrier properties

Multilayer film



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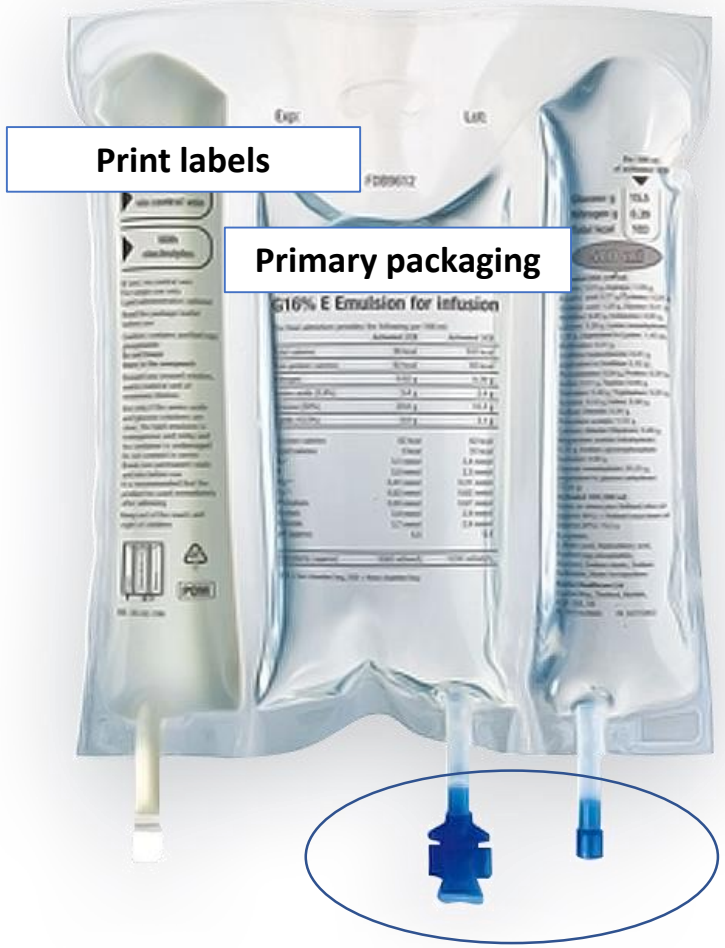
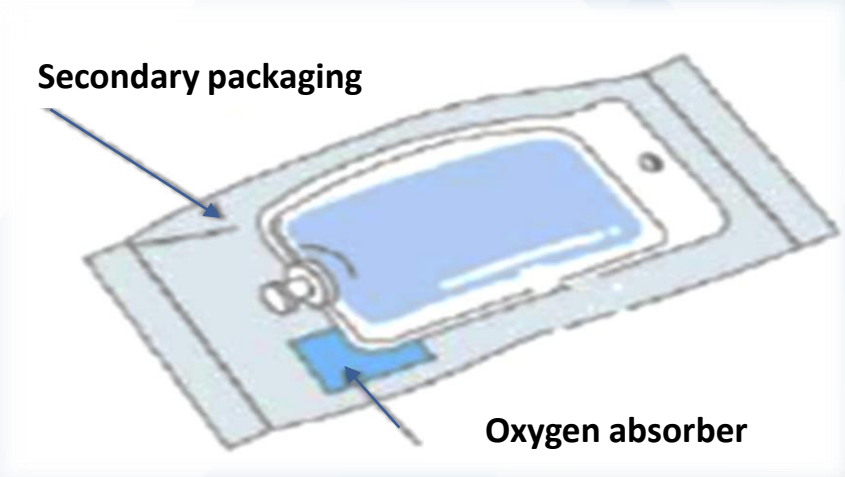
LVP design components





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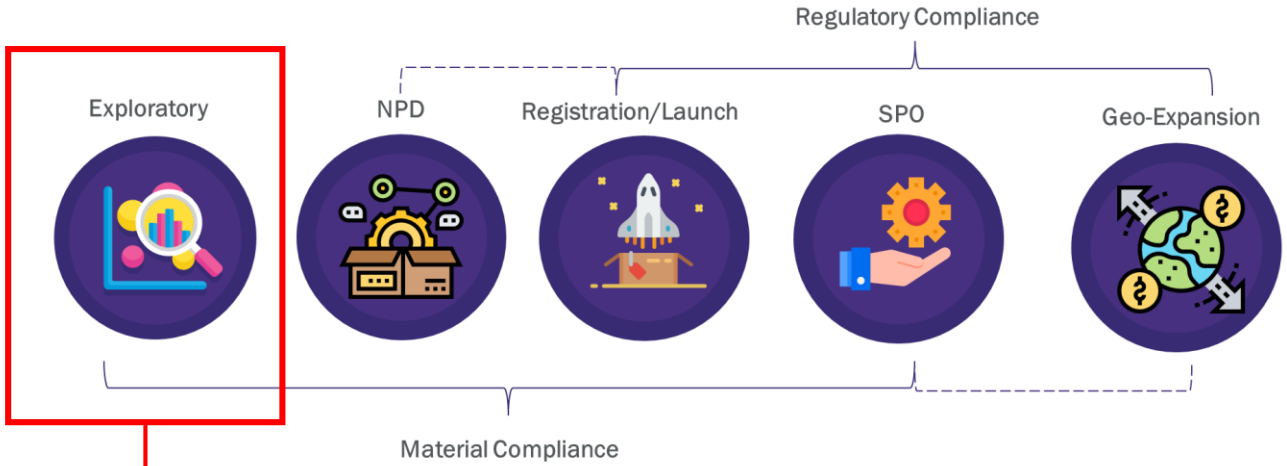
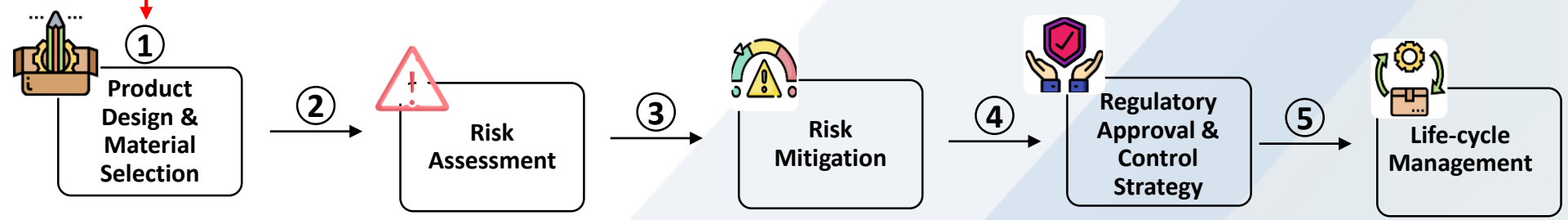
E&L strategy

Scope: at each stage of the product's lifecycle





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Material selection

Don’ts

- Miss the opportunity to get involved in the project at an early stage
- Underestimate the importance of Supplier’s data
- Avoid investing in preliminary testing

Do’s

- Engage with the supplier
- Collect all the relevant info related to the design and the application of the LVP product
- Thorough screening of required material to feed the risk assessment

Screening and Materials Selection | ELSIE (elsiedata.org)

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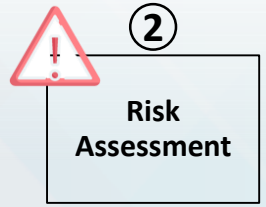
E&L Risk assessment



Consider the:

1. Package's materials of construction
2. Package formats (SA/ Volume)
3. Drug chemistry
4. Manufacturing
5. Shelf life
6. Clinical use
7. Patient population
8. Dosage and treatment period
9. Country of release

[Risk Control-Knowledge Gathering | ELSIE (elsiedata.org)]

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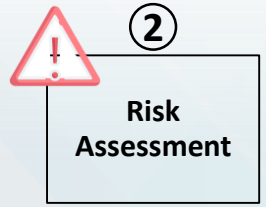
E&L supporting data



General info: e.g of **s**upplier info for materials used in LVP

Material info, Critical

- ❑ Material physio-chemical description
- ❑ Material Safety data sheet

Material info, Important

- ❑ Certificate of analysis
- ❑ Info about manufacturing

Material info, Supportive

- ❑ Material extractable data
- ❑ Material heavy metal content
- ❑ Comparability results

[Risk Control-Knowledge Gathering | ELSIE (elsiedata.org)]

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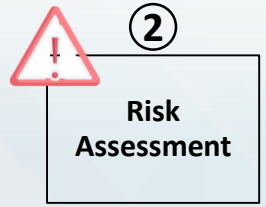
E&L supporting data



Safety Data: e.g of supplier info for materials used in LVP

Safety data, Critical

- ❑ REACH (1907/2006/EC)
- ❑ EU 94/TSE/BSE requirement per 2003/32/EC
- ❑ Certificate of absence of:
  - ❑ Bisphenol A
  - ❑ Phthalates (DEHP, DnHP,…)
  - ❑ Natural latex
  - ❑ PBTs
  - ❑ Nitrosamines
  - ❑ MBT
  - ❑ PAH
- ❑ Biocompatibility data per USP <88>, <87>

Safety data, Important

- ❑ SVHC per REACH and ECHA
- ❑ EC 1272/2008 CMR
- ❑ Biocompatibility data per USP <87>

Safety data, Supportive

- ❑ California Proposition 65
- ❑ PAAS

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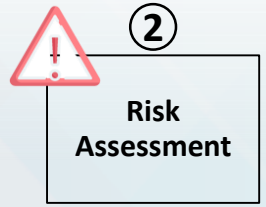
E&L supporting data



Regulatory data: e.g of supplier info for materials used in LVP

Regulatory data, Critical

- ❑ EU 2023/2006
- ❑ EU 2002/72/E
- ❑ 21CFR 172-189
- ❑ EP 3.1
- ❑ USP 661.1
- ❑ ISO 10993-5/6/10/11
- ❑ 21 CFR 177-1520 (additive)
- ❑ 21 CFR 175.105 (adhesive)

Regulatory data, Important

- ❑ **EU 10/2011 and amendments EU 202/2014** (monomers/additives)
- ❑ EP 3.2
- ❑ USP 381 (rubber)
- ❑ 21 CFR 175.300 (ink)
- ❑ EU 10/2011 (ink)
- ❑ EU 94/62/EC (heavy metals)
- ❑ EC 1935-2004

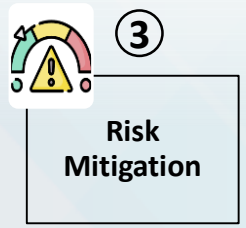
Regulatory data, Supportive

- ❑ USP 661.2
- ❑ Heavy metals per ICH Q3D
- ❑ EP 3.1.7

LVP: E&L study design





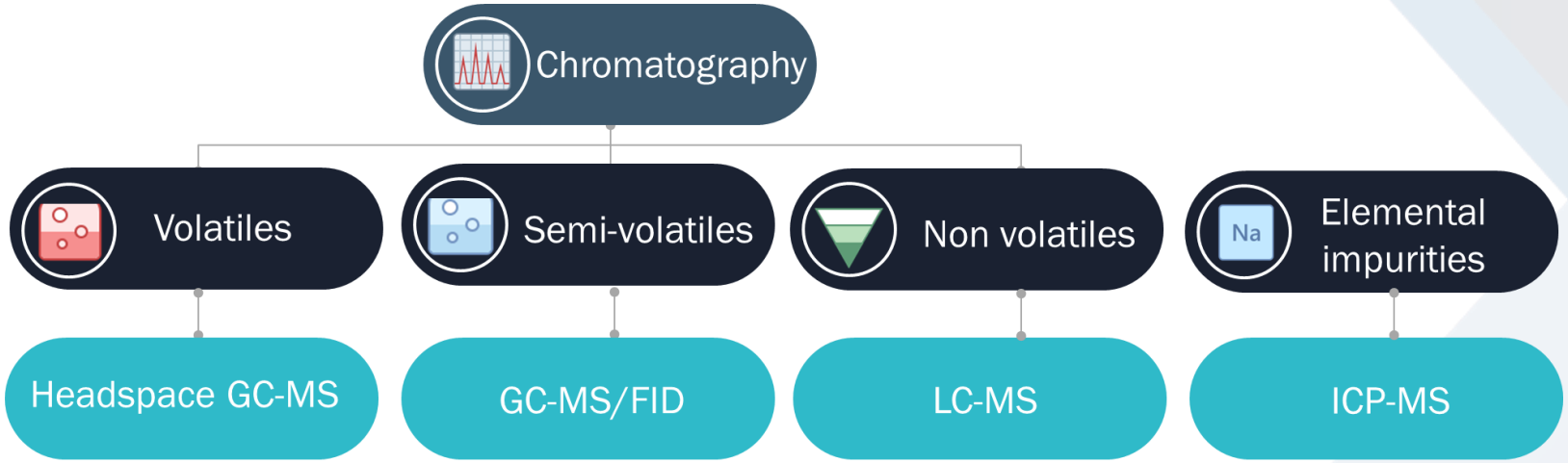



- Selecting test article → Material/solvent ratio
- Defining of AET → worst case MDD
- Selecting extraction solvents → simulation of drug chemistry
- Defining extraction time & accelerated storage → Clinical use & storage conditions
- Defining sterilization conditions → worst case cycle type and duration
- Selecting analytical technique → sensitive and accurate

LVP: Extractable testing

3

Risk Mitigation



Screening UNVALIDATED methods

Results > AET

Tox Assessment

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LVP: leachable strategy






Depending on Toxicological assessment and the resultant Margin of safety (MoS)

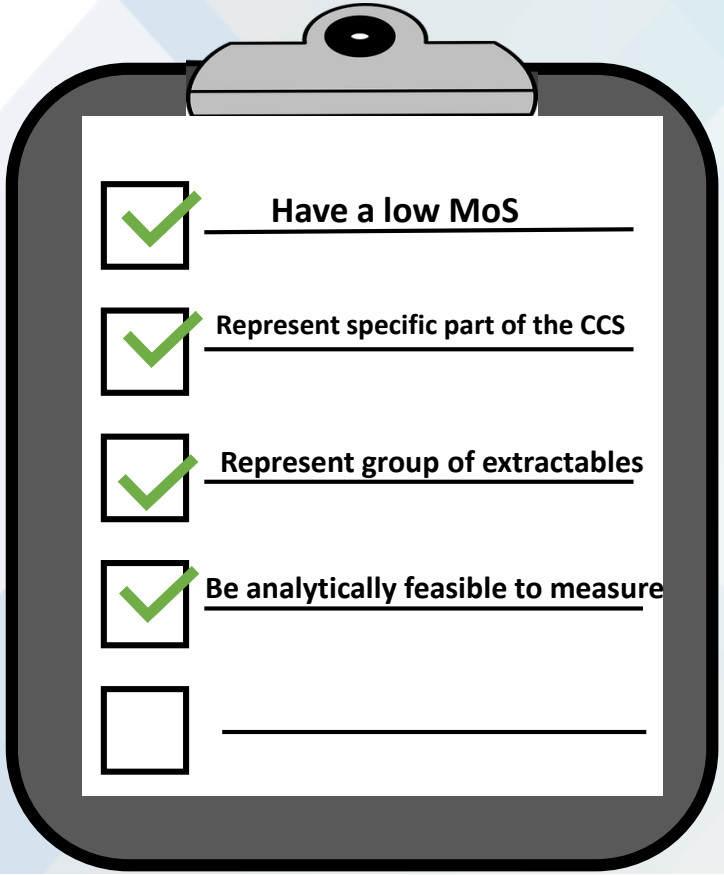
Scenario 1: High MoS → Execute a Leachable study on the drug product (stability batches) to <u>demonstrate product safety</u>

Scenario 2: Low MoS → Develop methods for targeted leachables to <u>put controls in place</u>

1. Feasibility study on the finished product (matrix effect)
2. Validated method per (ICH Q2)
3. Monitor targeted leachables during stability

④ Regulatory Approval & Control Strategy

Target Leachable must:



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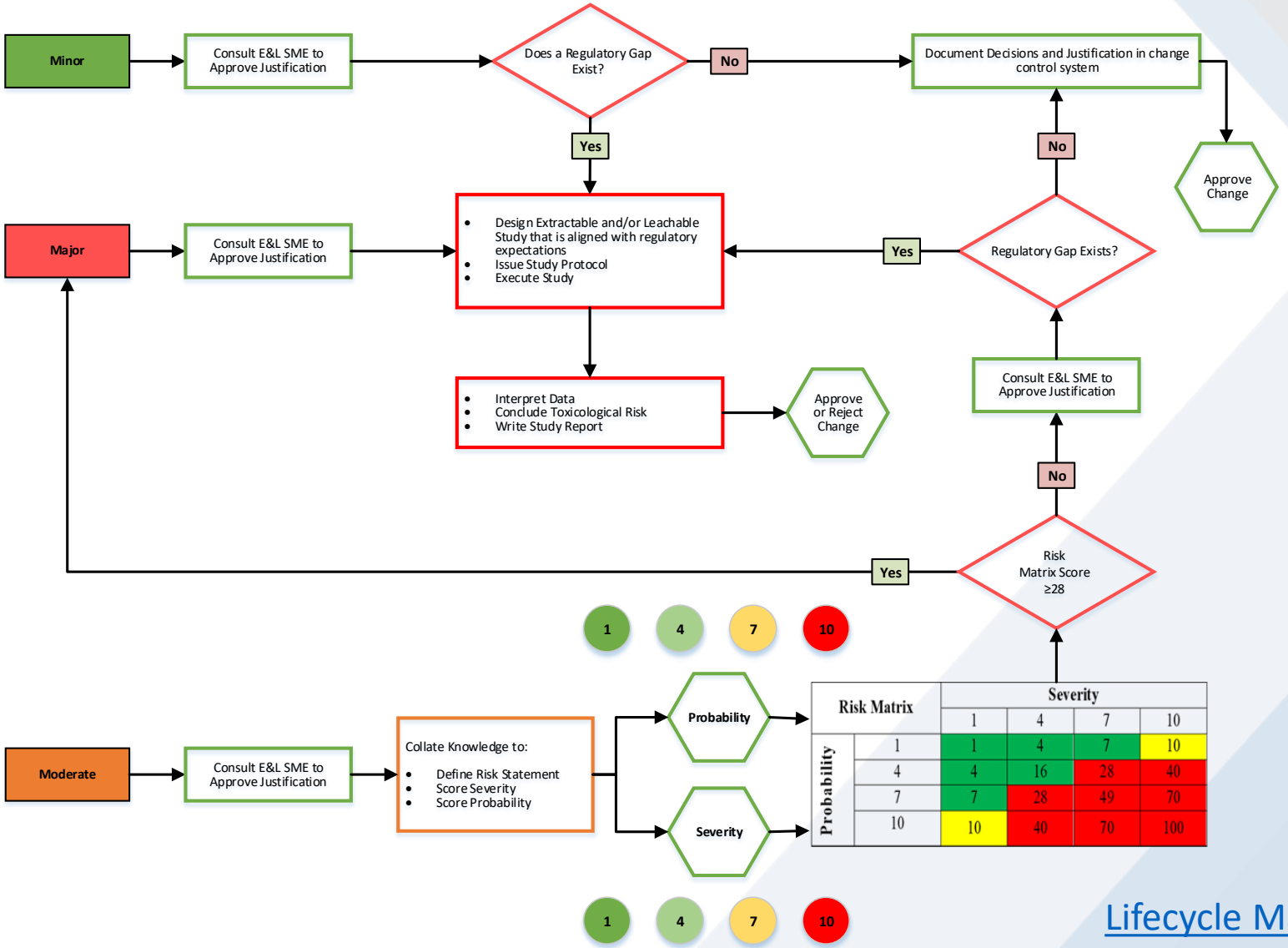
LVP Life cycle



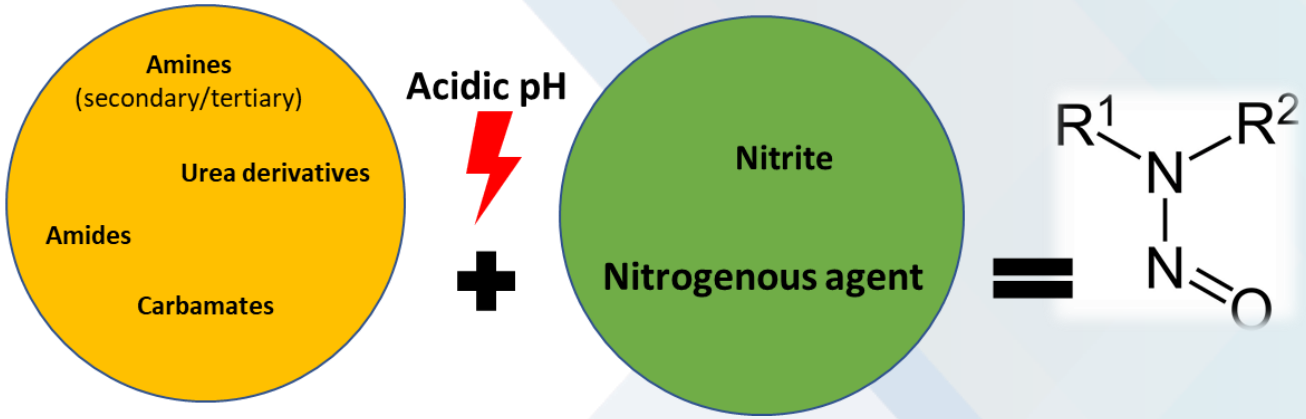
- ✓ Apply the same E&L strategy for upcoming change controls
- ✓ Leverage existing data and collected knowledge from suppliers
- ✓ Apply risk-based approach to handle changes

[Lifecycle Management | ELSIE (elsiedata.org)]

Source of risk matrix: SO/IEC Guide & ICH Q9

Fantastic Nitrosamine & how to find them?

Potential sources in LVP



1. **Solution**
    a. Raw materials (API and excipient)
    b. Synthesis process of the raw material
2. **Packaging system**
    a. Raw materials of plastic container, closures, printing (foil/ink), rubber
    b. Manufacturing process
3. **Drug Manufacturing process**
    a. Water quality of the plant (presence of Nitrite)
    b. Use of solvents or presence of residual solvent
    c. Mixing
    d. Sterilization

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Fantastic Nitrosamine & how to find them?

Nitrosamine Guidance per EMA/409815/2020 & USP <1469>

- **Step 1**: 31st Mar 2021

Risk evaluation & Identification of active substances & finished products

- **Step 2**: 26th September 2022

Confirmatory testing with validated analytical methods

- **Step 3**:

Potential update of marketing autorisation in case of changes in manufacturing process, raw materials or packaging

Source: "Maybe" means "No" - quickmeme

Nitrosamine in LVP

Potential risk → Screening study to identify root cause

Nitrosamine detection limit: 30% AET

$$\textbf{AET} = \frac{AI\ ng/day}{MDD\ (\frac{L}{day})}$$

AI is derived for singular Nitrosamine from EMA guidance **if** multi-Nitrosamines are expected the AI of the most potent molecule should be applied

MDD should be used based on the value in the SmPC file

Nitrosamine compound	Acceptable intake (AI in ng/day) EMA	Acceptable intake (AI in ng/day) FDA
NDMA	96.0	96
NDEA	26.5	26.5
EIPNA	26.5	26.5
DIPNA	26.5	26.5
NMBA	96.0	96
MeNP	26.5	
NDBA	26.5	
NMPA	34.3	26.5
Other	18	

Worst-case scenario: 30% AET

30% of $\frac{18\ ng/day}{2\ (\frac{L}{day})}$ = **2.7 ng/L**

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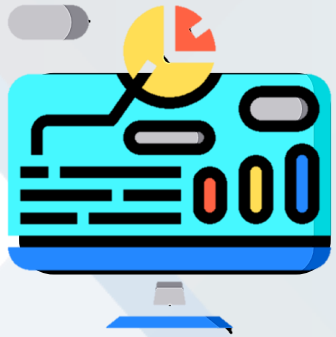
Source: EMA/409815/2020

Nitrosamine in LVP

Extraction

Concentration

Spike



Analysis LC MS/MS

Confirmatory testing:

Method: Validated method

- selectivity of the method should be demonstrated at the LoQ for each nitrosamine.

Test articles: Finished product

Reporting Data:

$$MoS = \frac{AI\ (Most\ potent)}{\sum all\ detecetd\ nitrosamines}$$

If MoS is low a change of raw material is required

Control strategy

If the source of risk has been identified and is well understood → 10% of the annual batches should be tested

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Source: EMA/409815/2020

Take home messages

E&L SME involvement of LVP design will ensure robust and successful qualification when proper E&L risk assessment strategy is followed.

Appropriate E&L study design coupled with material knowledge is vital for qualifying LVP.

Managing LVP life cycle by putting E&L control strategies in place.

Call To Action: Effective collaboration between medicinal companies & Material suppliers will facilitate tackling E&L challenges of LVP.

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