MINISTRY OF INDUSTRY AND TRADE OF RUSSIA

GMP VIII ALL-RUSSIA GMP CONFERENCE

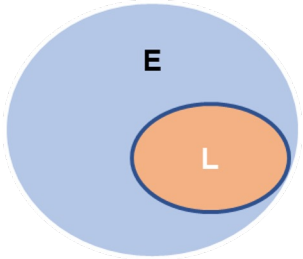
50 years GXP SID& GP

Extractables and leachables (E&L): requirements and approaches

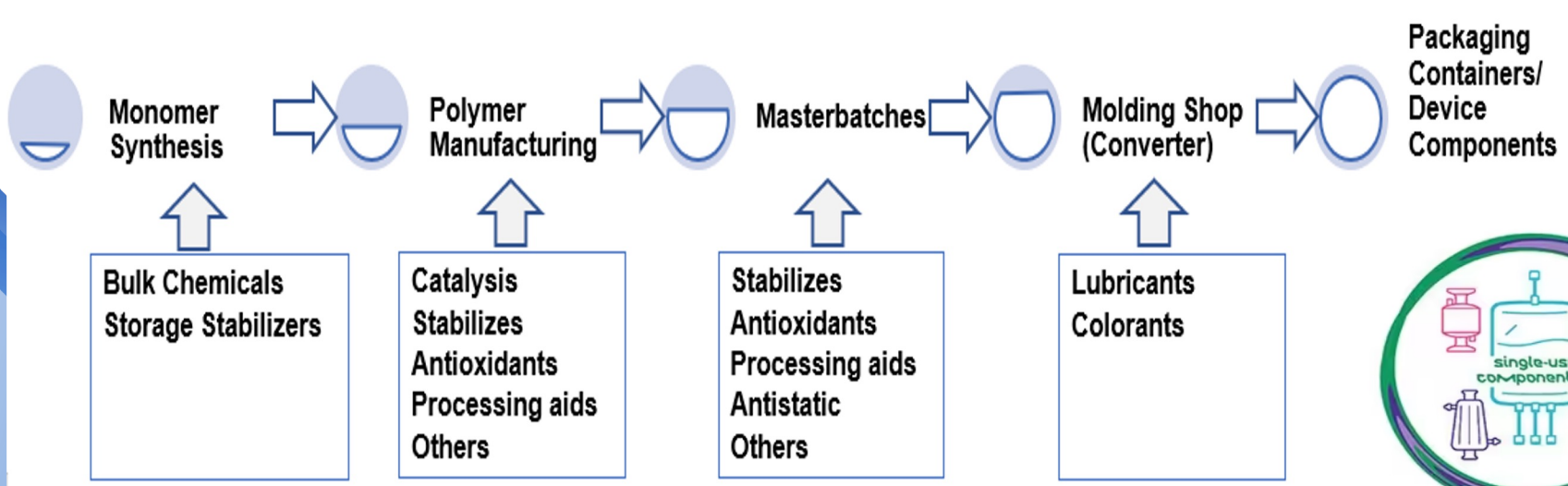
E&L: Sources, Terms and Definitions

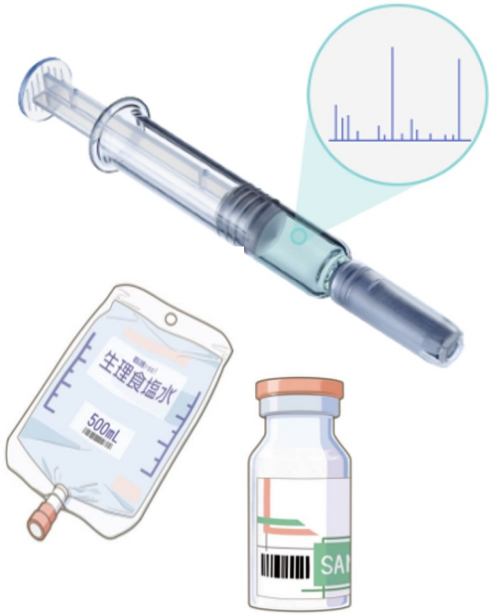
ICH impurity standards: Q3A, Q3B, Q3C, Q3D и M7.
A new guideline ICH **Q3E Assessment and Control of Extractables and Leachables (E&L) for Pharmaceuticals and Biologics** will be approved in November 2025

Extractables (E) are chemical entities, both organic and inorganic, that will extract from components of a container closure system or device into solvents under controlled conditions. They are used to identify and quantify potential leachables



Leachables (L) are chemical entities, both organic and inorganic, that migrate from components of a container closure system or device into a drug product over the course of its shelf-life. Leachables (L) is a subset of the extractables (E)





Regulations

- US Pharmacopeia <87> BIOLOGICAL REACTIVITY TESTS, IN VITRO , <88> BIOLOGICAL REACTIVITY TESTS, IN VIVO, <661.1> MATERIALS, <661.2> PACKAGING, <661.3> MANUFACTURING SYSTEM, <661.4> DEVICES,<1663> EXTRACTABLES , <1664> LEACHABELS, <1665> TOXICOLOGICAL ASSESMENT (https://www.usp.org)

- FDA Guidance for Industry "Container Closure Systems for Packaging Human Drugs and Biologics," May 1999 (www.fda.gov)

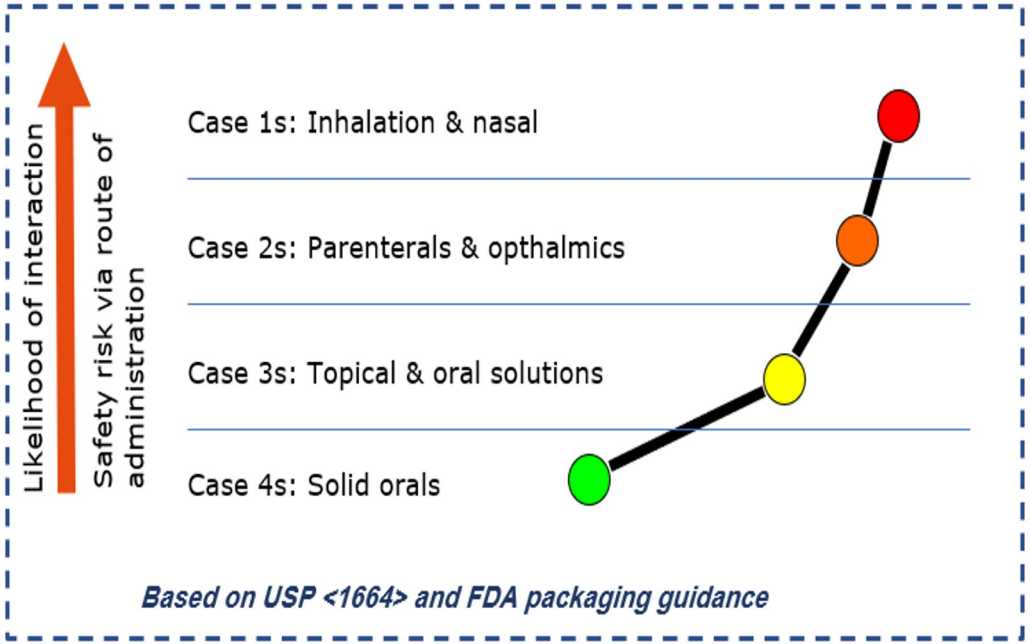
- EMEA, CPMP/QWP/4359/03 "Guideline on plastic immediate packaging Materials," London, May 19, 2005. (www.emea.europa.eu)

- Product Quality Research Institute (www.pqri.org). "Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products," Sept 8, 2006. «Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular)» October 28, 2021.

- Extractables and Leachables Concept (*www.elsiedata.org*)

- EAEC RECOMMENDATION No. 17 dated September 7, 2018 "On the Quality Guidelines for medicinal products for inhalation and nasal medicinal products (https://eec.eaeunion.org)

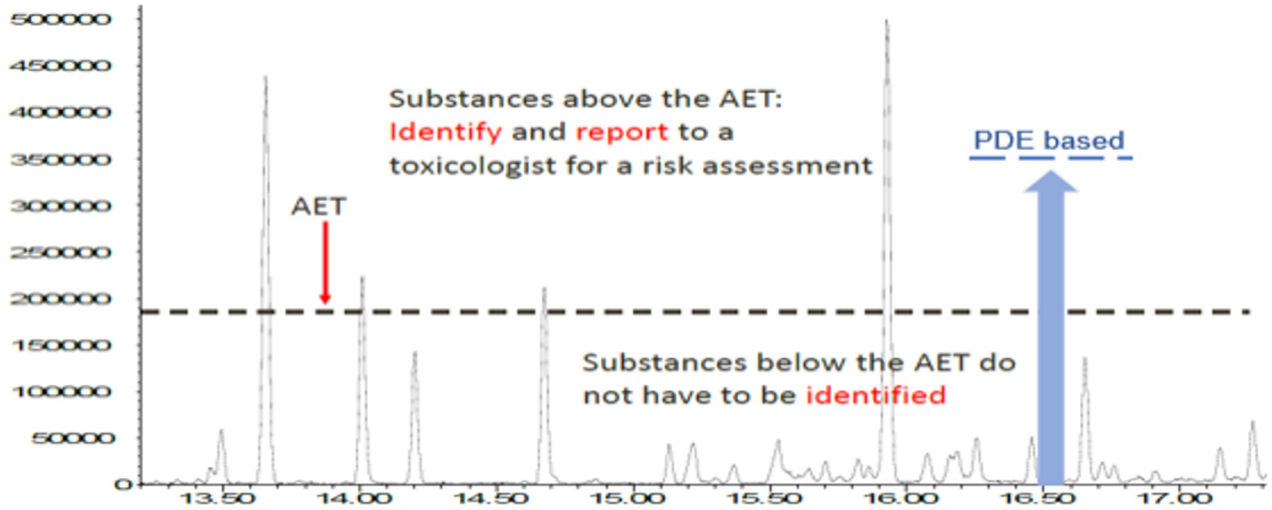
Risk-based approach and safety thresholds



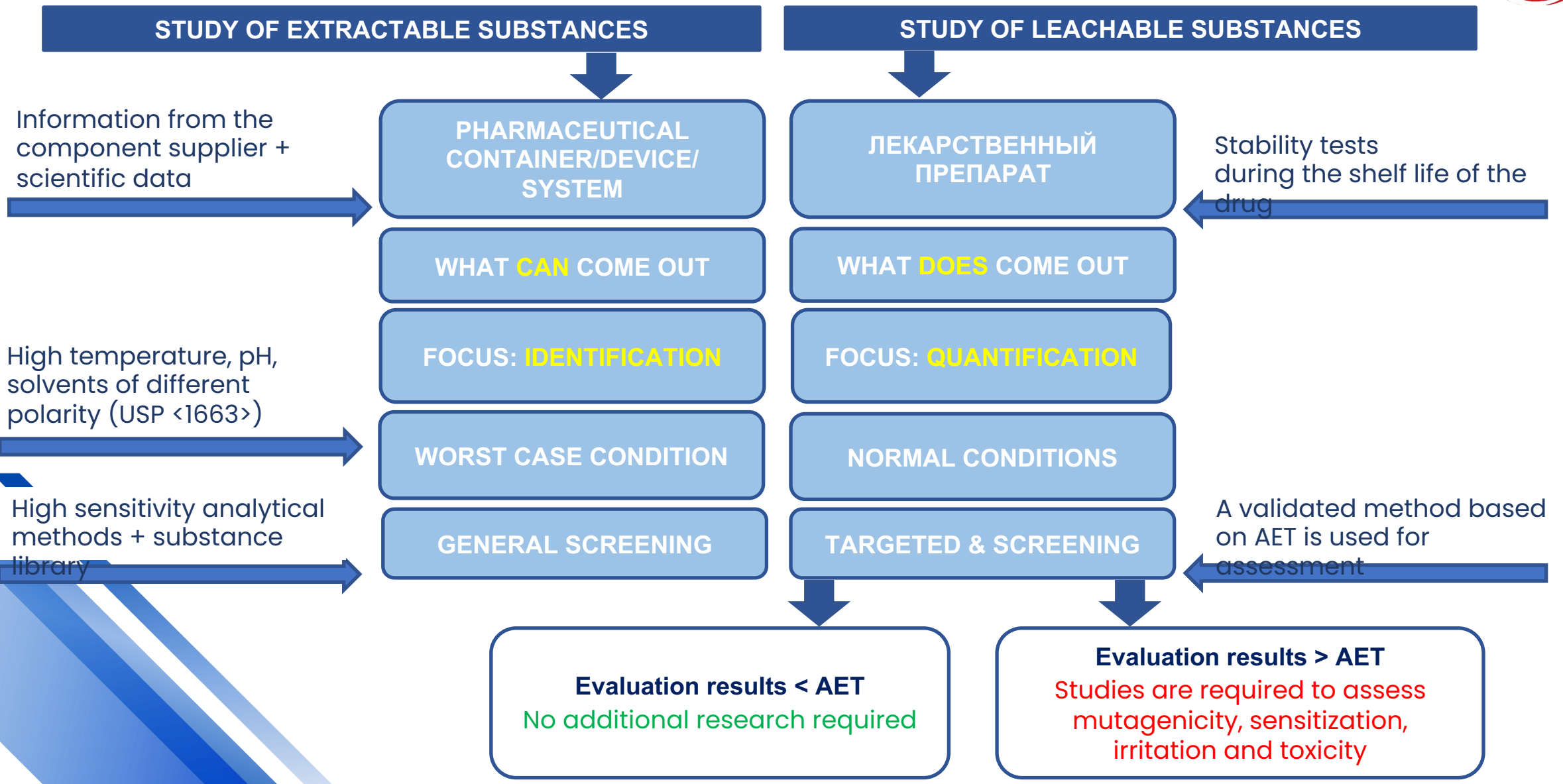
SCT	The Safety Concern Threshold - is the dose (0.15 µg/day) below which a **(L)** would present negligible concern for adverse carcinogenic and noncarcinogenic effects. *Acceptable daily intake for a carcinogen (see PQRI)*
AET	Analytical Evaluation Threshold – is the level at or above which should identify and quantify a particular **(E)** and/or **(L)** and report it for potential toxicological assessment. *Sensitivity of analytical method for leachables studies (see PQRI)*

Analytical Evaluation Threshold (AET) $\left(\frac{\mu g}{\text{container}}\right)$

$$= \frac{0{,}15 \mu g/day}{doses/day} * \frac{labeled\ doses}{container}$$



E&L testing concept



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