Promoting the Quality of Medicines

CLEANING VALIDATION WITH RISK ASSESSMENT

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Cleaning Validation with Risk Assessment

Presentation Outline:

- **Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment**
  - **US FDA Guide to Inspection of Validation of Cleaning Processes (1993)**
  - **US FDA Draft Guidance for Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients (1998)**
  - **APIC Guide "Cleaning Validation in Active Pharmaceutical Ingredient Manufacturing Plants (1999)" & Companion Document "Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants (2000)"**
  - **ICH Q7A Guidance for Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (2001) and ICH Q7 Revision 1 (2016)**
  - **ICH Q9 Quality Risk Management (2006)**
  - **ISPE Baseline Guide for The Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP) (2009)**
  - **EMA Guideline on Setting Health Based Exposure Limits For Use in Risk Identification in The Manufacture of Different Medicinal Products in Shared Facilities (2014)**
- **Cleaning Validation – How to Conduct with Risk Assessment Principles**

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **US FDA Guide to Inspection of Validation of Cleaning Processes (1993) - The Guide Cites ….**
  - **21 CFR 211.67 Equipment Cleaning and Maintenance Regulation.**
  - **Cholesteramine Resin Recall, Related To Contamination By "Tainted" Recovered Solvent Drums Used From Pesticide Facility In 1988**
  - **Incident in 1992, "Foreign" BPC (API) Manufacturer Produced Potent Steroids with Non-Steroid.. Did Not Perform Adequate Cleaning for Related Compounds.. - Leading To Contamination …..**
  - **Requires Written Procedures and Definition Of "Acceptable Level of Clean"**

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **US FDA Guide to Inspection of Validation of Cleaning Processes (1993) - The Guide Cites …. Continued**
  - **Prevent "Drying On" Of Residues on Dirty Equipment…..**
  - **Analytical Method Should be Validated to Evaluate % Recovery of API …..**
  - **Sampling Methods - Swabbing Preferred from Hardest To Clean Accessible Areas and "Dried On" Residues - Rinse Method Provides Advantage Of Reaching Inaccessible Areas**
  - **Refers to General Industry Approach [1] of Cleanliness Limits Suggested @10 ppm or 1/1000 Of Therapeutic Dose.**

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[1]- Apparent Reference to – "Fourman, G., and Mullin, M. , "Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations," Pharmaceutical Technology, April, 1993.

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **US FDA Draft Guidance for Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients (1998)**

  - **21 CFR Parts 210 & 211 Do Not Apply To API's - FDA Decided To Issue The Regulations As a Guidance Document**
  - **Dedicated Facility, Separate Air Handling & Dedicated Equipment, like for Penicillins, May Be Necessary for Cytotoxic & Other Hazardous Substances which Show Sensitization At Extremely Low Levels.**
  - **Matrix Approach Okay for Product Selection for Cleaning Validation - Use Of "Worst-Case" API Based on Potency, Toxicity, Solubility, and Difficulty Of Cleaning**

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **US FDA Draft Guidance for Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients (1998)**

  - **Sampling was recommended to Include Swabbing, Rinsing, or Alternative methods**
  - **Residue Limits were Recommended to be Practical, Achievable, Verifiable, and Based on the Most Deleterious Residue, Based on Pharmacological or Physiological activity of the API.**
  - **No Reference to Historical 10 ppm or 1/1000th of Dose Carryover Limit – Left it Up To the Industry to Justify Actual Limits.**
  - **US FDA Deferred to ICH Q7 Guidance, and Left Its Own Guidance as a Draft.**

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **APIC (A Sector Group of CEFIC) Guide "Cleaning Validation in Active Pharmaceutical Ingredient Manufacturing Plants (1999)" & Companion Document "Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants (2000)"**
  - **Defined Cleaning Validation (CV) for APIs as "The Process of Providing Documented Evidence That the Cleaning Methods Employed Within a Facility Consistently Controls Potential Carryover of Product (Including Intermediates and Impurities), Cleaning Agents and Extraneous Material Into Subsequent Product To a Level Which is Below Predetermined Levels."**
  - **CV Limit -1/1000th Therapeutic Daily Dose (TDD) of Previous Material Into the Next Product Batch TDD. Maximum Allowable Carryover (MACO) Limit-**

$$MACO = \frac{TDD_{previous} \times MBS}{SF \times TDD_{next}}$$

SF – Safety Factor – Normally for Oral Dosage is 100 to 1,000

Topicals is 10 to 100

Parenterals is 1,000 to 10,0000

MBS – Minimum Batch Size of the Next Product

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **APIC Guide – Continued**
  - **When No TDD Available, CV MACO Limit Based on Toxicity Data by Calculating the NOEL (No Observable Effect Level) Value**

$$NOEL = \frac{LD50\ (g/kg) \times 70\ (kg\ person)}{2{,}000\ (an\ Empirical\ Constant)}$$

$$MACO = \frac{NOEL \times MBS}{SF \times TDD\ next}$$

  - **When the Above Methods Result in Unacceptably High The Approach of a General Limit May be Suitable, such as 10 ppm Carry Over in the Next Product Batch.**
  - **The Surface Samples Swab Limit = MACO/Total Surface Area in Contact with Product in Equipment Train.**

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **ICH Q7A Guidance for Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (2001) and ICH Q7 Revision 1 (2016)**
  - **The CV Guidance Identical to That in the US FDA Draft API GMPs Guidance (1998)**
  - **Matrix Approach Okay for Product Selection for Cleaning Validation – Same Criteria as US FDA Draft Guidance**
  - **Sampling was recommended to Include Swabbing, Rinsing, or Alternative methods. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations**

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **ICH Q7A Guidance – Continued**
  - **Residue Limits were Recommended to be Practical, Achievable, Verifiable, and Based on the Most Deleterious Residue, Based on Pharmacological or Physiological activity of the API.**
  - **No Reference to Historical 10 ppm or 1/1000th of Dose Carryover Limit – <u>Left it Up To the Industry to Justify Actual Limits</u>**
  - **Revision 1 of the ICH Q7 (2016) the CV Recommendations Unchanged.**

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

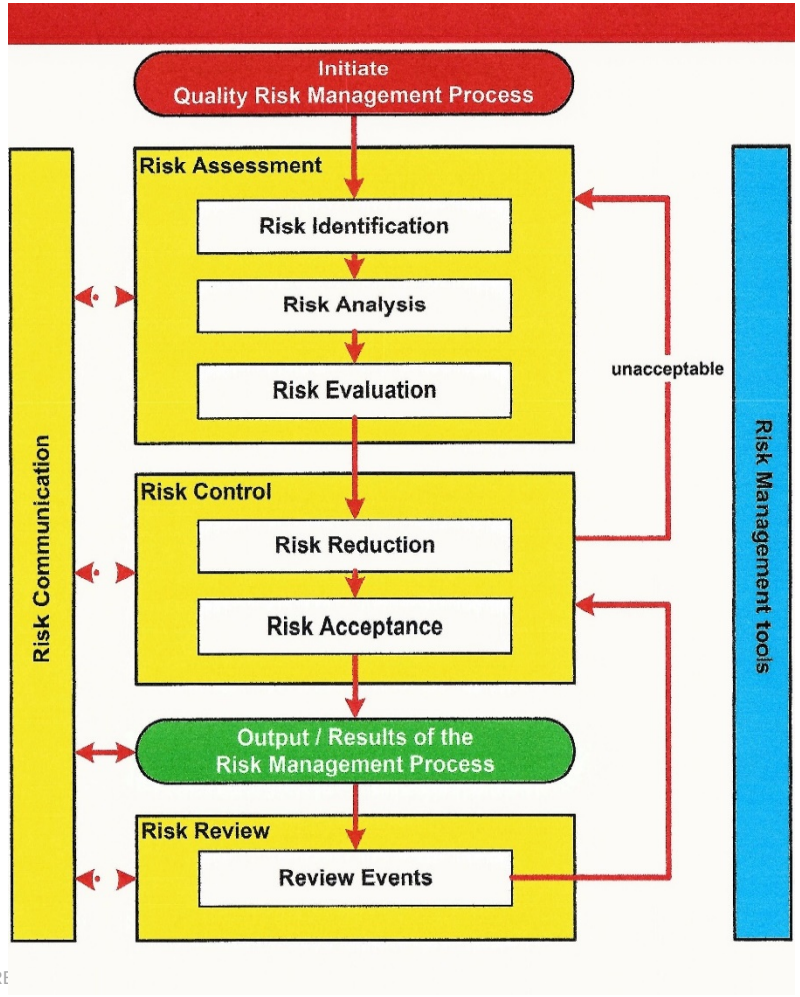
- **ICH Q9 Quality Risk Management (2006)**
  - **Risk Defined as The Combination of the Probability of Occurrence of Harm and the Severity of that Harm**
  - **The Purpose of this Guidance - Offer a Systematic Approach to Quality Risk Management (QRM)**
  - **QRM is a Systematic Process - Assessment, Control, Communication and Review of Risks to the Quality of the Drug Across its Lifecycle.**
  - **A Robust Process Will Incorporate Consideration of All The Elements At a Level of Detail That is Commensurate With the Specific Risk.**
  - **A Model For QRM is Outlined in The Diagram in The Next Slide**

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **ICH Q9 Quality Risk Management (2006) - Continued**

Quality Risk Management Flow Chart

(Borrowed from Alan Halstead Presentation at ISPE 2008 Annual Meeting)



Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **ICH Q9 Quality Risk Management (2006) – Continued**
  - **INITIATING A QUALITY RISK MANAGEMENT (QRM) PROCESS – Identify the Risk, Assemble Information, Assign a Leader to Address the Risk, Specify a Timeline, Deliverables, and Appropriate Level of Decision Making**
  - **CONDUCTING RISK ASSESSMENT - Consists of the Identification of Hazards Followed by the Analysis and Evaluation of Risks**
    - **Risk Identification Addresses the "What Might Go Wrong?" Question, this Provides the Basis For Further Steps in the QRM Process.**
    - **Risk Analysis addresses the Questions - What is the Likelihood (Probability) it Will go Wrong? And What are the Consequences (Severity)? It is the Qualitative or Quantitative Analysis of the Risk by Linking the Likelihood of Occurrence and Severity of Harms. In Some Risk Management Tools (Such as FMEA), The Ability to Detect the Harm (Detectability) Also Factors in the Estimation Of Risk.**
    - **Risk evaluation Compares the Identified and Analyzed Risk Against Given Risk Criteria. Risk Assessment Can be Quantitatively (RPN # in FMEA) or Qualitatively Summarized as High, Medium & Low**

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **ICH Q9 Quality Risk Management (2006) – Continued**
  - **RISK REDUCTION - Actions Taken to Mitigate the Severity and Probability of Harm (See Figure Above).**
  - **RISK ACCEPTANCE - Formal Decision to Accept the Residual Risk or Passive Decision in Which Residual Risks Are Not Specified. Some Risks Can Only be Reduced To an Acceptable Level.**
  - **RISK COMMUNICATION - Done at Any Stage of QRM Process (Dashed Arrows in Figure). The Final Output/Result of QRM Process Will be Communicated and Documented (Solid Arrow In Figure).**
  - **RISK REVIEW - Ongoing (Life Cycle) Part of QRM Process, With a Mechanism to Force Risk Review at Events (i.e., Change Control)**
  - **RISK MANAGEMENT METHODOLOGY - Industry and Regulators Can Assess and Manage Risk Using Published Risk Management Tools and/or Internal Procedures (E.G., Standard Operating Procedures). A List Of Some Of These Tools Provided in the ICH Q9 Guidance Listed on the Next Slide**

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- **Risk Management Facilitation Methods**
  - Basic Risk Management Facilitation Methods (Flowcharts, Check Sheets, etc.)
  - Failure Mode Effects Analysis (FMEA) - FMEA Can be Applied to Equipment and Facilities and Might Be Used to Analyze a Manufacturing Operation Study, Such as Cleaning Validation.
  - Failure Mode, Effects, and Criticality Analysis (FMECA)
  - Fault Tree Analysis (FTA)
  - Hazard Analysis and Critical Control Points (HACCP)
  - Hazard Operability Analysis (HAZOP)
  - Preliminary Hazard Analysis (PHA)
  - Risk Ranking and Filtering
  - Supporting Statistical Tools

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- **ISPE Baseline Guide for The Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP) (2009) – CV Related Highlights**
  - Risk MaPP Guide Provides a Risk Based Approach Based on ICH Q9 for Setting Health Based Cross-Contamination and CV Limits Within Multi-Product Facilities.
  - The Guide Provides a Health Based Tool to Identify Highly Hazardous Drugs and Fits it Into CV
  - Equipment Must be Consistently Clean to a Level Where the Risk Of Cross-Contamination Can be Shown to be Minimal and Acceptable.
  - CV Limits to be Based on the Acceptable Daily Intake (ADI) and Not a Fraction of the Therapeutic Dose, 10 ppm Carry-Over, LD50 or Other Toxicity Criteria.
  - The ADI is the Amount of a Chemical or API (mg/kg Body Weight) in Food, Drinking Water, or Product-to-Product Cross-Contamination that Can be Safely Ingested by Humans Each Day Over a Lifetime Without Appreciable Adverse Health Effect.

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- **ISPE Risk-MaPP – CV Related Highlights – Continued**
  - **CALCULATION OF THE ACCEPTABLE DAILY INTAKE (ADI)**

    $$\text{ADI (mg/day)} = (\text{NOAEL (mg/kg/day)} \times \text{BW (kg)})/(UF_C \times MF \times PK)$$
  - **CALCULATION OF HEALTH-BASED CLEANING LIMITS**

    $$\text{Swab Limit (Product Contact Surfaces) (mg/swab)} = \frac{\text{ADI (mg/day)} \times \text{Batch Size (mg)} \times \text{Test Area (cm}^2\text{)} \times \text{Recovery Factor}}{\text{MDD (mg)} \times \text{SSA (cm}^2\text{)}}$$

    $$\text{Rinse Concentration (mg/L)} = \frac{[\text{ADI (mg/day)} \times \text{SB (mg)} \times \text{Rinsed Area (cm}^2\text{)}]}{[\text{Volume of Rinse (L)} \times \text{MDD (mg)} \times \text{SSA (cm}^2\text{)}]}$$
  - **CALCULATION OF OCCUPATIONAL EXPOSURE LIMITS**

    $$\text{OEL (mg/ m}^3\text{)} = \text{ADI (mg/day)}/(10\ \text{m}^3\ \text{/day})$$

Where, ADI = Acceptable Daily Intake
NOAEL = No-Observed-Adverse-Effect-Level,
OEL = Occupational Exposure Limit
BW = Body Weight
UF_C = Composite Uncertainty Factor
MF = Modifying Factor
PK = Pharmacokinetic Adjustment(s)
MDD = Maximum Daily Dose
SSA = Shared Surface Area
SB = Smallest Batch Size

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **ISPE Risk-MaPP – CV Related Highlights – Continued - Criticism of the Risk-MaPP Guide**

  - **A. Walsh[2] Points Out That From Risk-MaPP Definition, The ADE is a Very Conservative Value. Thus Possibly Artificially Reducing The Cleaning Limit Based on ADE as Defined in the Risk-MaPP.**
  - **The Risk-MaPP Was Developed For "Compounds Of Concern", These "Classes" of Compounds Were to Include Hormones, Cytotoxic Compounds, Genotoxic Compounds, Live Vaccines, and Sensitizers Such as Antibiotics Including Beta-Lactams. ISPE Was to Develop a Tool to Identify Highly Hazardous Drugs and Discuss How that Tool Can be Made to Fit the CV of These Hazardous Compounds. In Practice, the ADE Based Cleaning Limit by Default is Expected of Every Compound.**

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[2]- Walsh, A. "Cleaning Validation for the 21st Century: Acceptance Limits for Active Pharmaceutical Ingredients (APIs): Part II," Pharmaceutical Engineering, September/October 2011, Volume 31, Number 5, pp. 44-49

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **ISPE Risk-MaPP – CV Related Highlights –**

  Criticism of the Risk-MaPP Guide – Continued

  - **The Risk-MaPP Seems to be Favoring the Innovator Companies, Since All The Safety, Efficacy And Toxicology Data Necessary to Calculate NOAEL and ADE Have Been Already Developed for Their NDA. The ANDA and WHO-PQ Applicants Do Not Have Access to The Innovator NDA Data, and Have to Hire CROs/Toxicologists to Develop The Information From Published Literature, Which Could Be Incomplete and Misleading.**
  - **D. A. Leblanc[3], in a Cleaning Memo Stated That "The Effort Of The Risk-MaPP Team Should Not Have Been to Critique Current Methods of Setting Limits (Such as 10 ppm or 1/1000th of a Dose Carryover) for Actives In General, But They Should Have Focused Their Critique On Current Methods Of Setting Limits For "Highly Hazardous" Actives".**

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **EMA Guideline on Setting Health Based Exposure Limits For Use in Risk Identification in The Manufacture of Different Medicinal Products in Shared Facilities (2014)**
  - **The Chapters 3 and 5 of the EMA GMP Guideline Have Been Revised to Promote a Science and Risk-Based Approach and Refer to a "Toxicological Evaluation" For Establishing Threshold Values for Risk Identification.**
  - **Review and Evaluate Pharmacological and Toxicological Data of Individual Active Substances (Implied – for Hazardous Compounds) and Determine Threshold Levels as Referred to in the GMP Guideline. These Levels then Can be Used as a Risk Identification Tool to Calculate the Carry Over Limits Used in CV**

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessmen

- **EMA Guideline on … Continued –**
  - **Review of All Available Animal and Human Data For Hazard Identification Would Include Non-clinical Pharmacodynamic Data, Repeat-Dose Toxicity Studies, Carcinogenicity Studies, *In-Vitro* and *In-Vivo* Genotoxicity Studies, Reproductive and Developmental Toxicity Studies as Well as Clinical Data (Therapeutic and Adverse Effects).**
  - **Permitted Daily Exposure (PDE) Represents a Substance-Specific Dose that is Unlikely to Cause an Adverse Effect if an Individual is Exposed at or Below this Dose Every Day For a Lifetime (Similar to ADE Defined in Risk-MaPP Guide)**

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **EMA Guideline on….. - Continued**
  - **Appendices 3 of the ICH Q3C and VICH GL 18 Guidelines Present the Following Equation for the Derivation of the PDE:**

$$PDE = \frac{NOAEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

The NOAEL is the Highest Tested Dose at Which No "Critical" Effect is Observed. If The Critical Effect is Observed in Several Animal Studies, the NOAEL Occurring At The Lowest Dose Should be Used For Calculation of The PDE value.

If no NOAEL Is Obtained, the Lowest-Observed-Adverse-Effect Level (LOAEL) May be Used.

Factors F1 to F5 are Addressing The Following Sources Of Uncertainty:

F1: A Factor (Values Between 2 and 12) to Account for Extrapolation Between Species

F2: A Factor of 10 to Account for Variability Between Individuals

F3: A Factor 10 to Account for Repeat-Dose Toxicity Studies of Short Duration, i.e., Less Than 4-weeks

F4: A Factor (1-10) That May be Applied in Cases of Severe Toxicity, e.g., Non-Genotoxic Carcinogenicity, Neurotoxicity or Teratogenicity

F5: A Variable Factor That May be Applied if the No-Effect Level Was Not Established. When Only a LOAEL (Lowest-Observed-Adverse-Effect Level) is Available, a Factor of Up To 10 Could be Used Depending on The Severity of the Toxicity.

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **Questions and Answers on Implementation of Risk Based Prevention of Cross Contamination In Production and 'Guideline on Setting Health Based Exposure Limits (HBEL) for Use in Risk Identification in The Manufacture of Different Medicinal Products in Shared Facilities' (EMA/CHMP/CVMP/SWP/169430/2012) – Q&A Issued January 2017 for Public Consultation – Until 30 April, 2017**

- **Q2. What Products/Active Substances are Considered to be Highly Hazardous?**

  A. Highly Hazardous Products are those that Can Cause Serious Adverse Effects at Low Doses and that Therefore Would Benefit From a Full Toxicological Assessment in Order to Derive a Safe HBEL. Evidence Indicating a Product or Active Substance Falls Within Any of the Categories Below Should Result in a Product Being Considered Highly Hazardous (Next Slide)

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **Q and A on Implementation of Risk Based ….. (EMA/CHMP/CVMP/SWP/169430/2012) – Continued**

1. **Genotoxic (Specifically Mutagenic) Compounds that are Known to be, or Highly Likely to be, Carcinogenic to Humans …….**
2. **Compounds that can Produce Reproductive and/or Developmental Effects at Low Dosages ……..**
3. **Compounds that can Produce Serious Target Organ Toxicity or Other Significant Adverse Effects at Low Doses ……**
4. **Compounds with a High Pharmacological Potency i.e. Recommended Daily Dose of <1 mg (Veterinary Dose Equivalent 0.02 mg/kg)**
5. **Compounds with a High Sensitising Potential.**

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **Q and A on Implementation of Risk Based ….. (EMA/CHMP/CVMP/SWP/169430/2012) – Continued**

  - **Q3. Could Occupational Exposure Limits (OELs) or Occupational Exposure Bands (OEBs) be Used to Support Assessment of Products to Determine Whether They May be Highly Hazardous?**

    A: Yes. Extrapolation of an OEL a Preliminary Permitted Daily Exposure (PDE) Can be Simply Done by Using the Following Formula:

    PDE (µg/day) = OEL (µg/ m^3) x 10 m^3 (the volume air breathed by a worker in 8 hours).

    If the Resulting PDE Value is 10 Mg/Day or Lower the Product Should be Considered as Highly Hazardous.

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **Q and A on Implementation of Risk Based ….. (EMA/CHMP/CVMP/SWP/169430/2012) – Continued**

  - **Q4. Can Calculation of HBELs be Based on Clinical Data Only (e.g. to Establish the HBEL on 1/1000th of the Minimum Therapeutic Dose)?**

    A: For….Products…(that)…Have a Favourable Therapeutic Index, the Therapeutic Dose Information Could be Used as the 'Point of Departure' for Calculation of the HBEL (e.g. the PDE). Under these Circumstances, HBEL Based on the 1/1000th Minimum Therapeutic Dose Approach Would be Considered as Sufficiently Conservative and Could be Utilised for Risk Assessment and Cleaning Purposes.

Regulatory History and Guidelines Evolution of Cleaning Validation and Risk Assessment

- **Q and A on Implementation of Risk Based ….. (EMA/CHMP/CVMP/SWP/169430/2012) – Continued**

  - **Q5. Is the Use of LD50 to Determine Health Based Limits Acceptable?**

    A: No, LD50 is Not an Adequate Point of Departure to Determine a HBEL.

  - **Q6. How Can Limits for Cleaning Purposes be Established?**

    A: Although the EMA Guideline (EMA/CHMP/CVMP/SWP/169430/2012) May be Used to Justify Cleaning Limits, Traditional Cleaning Limits Used by Industry Such as 1/1000th of Minimum Therapeutic Dose or 10 ppm of One Product in Another Product, May Accomplish this for Non-Highly Hazardous Products. (Improvement Over Risk-MaPP Guide)

    For Products Classed as Highly Hazardous, Where a Thorough Risk Assessment Can Justify Manufacture in Shared Facilities, Cleaning Limits Should Include Safety Factors Beyond the HBEL and Should Not be Higher Than the Traditional Cleaning Limits Approach.

Cleaning Validation – How to Conduct with Risk Assessment Principles

- **CV Protocol – Examples of Employing Risk-Based Approach**

  Employ any of the Tools for Risk Assessment, i.e., FMEA, For Each of the Requirement of the CV Study Protocol - Identify the Risk, Propose the Mitigation Strategy and Evaluate the Risk Score Before and After Successful Mitigation Strategy Execution. Document This Exercise in the CV Protocol.

  - **Create a Grouping of Products/APIs Manufactured on the Same Equipment Train**

    Risk – You wish to Minimize CV Study to One Product/API for Each Equipment Train. Score the Risk as High Before Mitigation Strategy in the Protocol

    Mitigation Strategy – Identify the "Worst Case" Product/API Considering the Solubility, Hardest to Clean and Toxicity and Develop a Detailed Cleaning Procedure for that Product/API to be Validated. Score the Risk as Low Theoretically in the Protocol if Your CV Study Would be Successful with the Worst Case Product/API. If the CV Study Meets the Acceptance Criteria, You Have Successfully Used the Risk-Based Approach

Cleaning Validation – How to Conduct with Risk Assessment Principles

- **CV Protocol – Examples of Employing Risk-Based Approach – Continued**

  - **Demonstrating Repeatability of Cleaning with the Cleaning Method Being Manual, Semi-Automatic or Automatic (CIP)**

    Risk – the Hardest to Validate Would be a Manual Cleaning Method - Score the Risk as High Before Mitigation in the Protocol,

    Mitigation Strategy - Develop a Very Detailed Step-by-Step SOP/Work Instruction for the Manual Cleaning, with Requirement for Operator Testing & Retraining, Train the Operators and Document the Training. Score the Risk as Low Theoretically if Your CV Study is Successful with the SOP-Trained Operators Conducting the Manual Cleaning for Typically Three (3) CV Batches. If the CV Study Meets the Acceptance Criteria, You Have Successfully Used the Risk-Based Approach

Cleaning Validation – How to Conduct with Risk Assessment Principles

- **CV Protocol – Examples of Employing Risk-Based Approach – Continued**
  - **Qualifying Dirty Equipment Hold Time**

Risk – the Residue Will be Dried on the Equipment Surfaces and Will be Hard to Clean, Especially with a Manual Cleaning Method

Mitigation Strategy - Develop a Very Detailed Step-by-Step SOP/Work Instruction for the Manual Cleaning, with Requirement for Testing & Retraining, Train the Operators and Document the Training. Score the Risk as Low Theoretically if Your CV Study is Successful with the SOP Trained Operator Conducting the Manual Cleaning for Typically Three (3) CV Batches. If the CV Study Meets the Acceptance Criteria, You Have Successfully Used the Risk-Based Approach

Cleaning Validation – How to Conduct with Risk Assessment Principles

- **CV Protocol – Examples of Employing Risk-Based Approach – Continued**
  - **Cleaning Limit**

    Risk – CV Study Will Need to Demonstrate That the Cleaning Method Employed for the Equipment Train to be Studied for CV Consistently Controls Potential Carryover of Product, Cleaning Agents and Extraneous Material Into Subsequent Product To a Level Which is Below Predetermined Levels. The Cleaning Limit Will Need to be Justified as the Most Stringent Criteria from Industry Current Standards.

    Mitigation Strategy – For the Compound/s Under the CV Study, Calculate the Cleaning Limit for the Contaminant Product Into the Subsequent Product of the Smallest Batch Size by a General Limit Method (i.e., 10 ppm Carryover), A HBEL Toxicology Based (ADI/PDE) Method (Especially if the Product is Hazardous) and a Therapeutic Dose Based (i.e., 1/1000th of the Smallest Dose) Method. Select the Lowest Limit for the CV Study, Thus, Minimizing Health Based Risk. If the CV Study Meets the Acceptance Criteria, You Have Successfully Used the Risk-Based Approach

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