CLEANING VALIDATION
RELATERET TIL ANNEX 15 OG LIDT ANDET

Symbion
IFF QA ERFA 2015-10-06
**ECA: Quo vadis Cleaning Validation in Annex 15?**

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[http://www.eca-foundation.org](http://www.eca-foundation.org)

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ANNEX 15 - PRINCIPLE

- This Annex describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products and may also be used as supplementary optional guidance for active substances without introduction of additional requirements to EudraLex, Volume 4, Part II. It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process. Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed. Computerised systems used for the manufacture of medicinal products should also be validated according to the requirements of Annex 11. The relevant concepts and guidance presented in ICH Q8, Q9, Q10 and Q11 should also be taken into account.
• A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes. Retrospective validation is no longer considered an acceptable approach. Data supporting qualification and/or validation studies which were obtained from sources outside of the manufacturers own programmes may be used provided that this approach has been justified and that there is adequate assurance that controls were in place throughout the acquisition of such data.
Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment. Simulating agents may be used with appropriate scientific justification. Where similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected.
ANNEX 15 – CV 10.2

• A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation. It is not generally acceptable for this criterion alone to be used. Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach.
It is recognised that a cleaning validation programme may take some time to complete and validation with verification after each batch may be required for some products, e.g. investigational medicinal products. There should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.
ANNEX 15 – CV 10.4

- Validation should consider the level of automation in the cleaning process. Where an automatic process is used, the specified normal operating range of the utilities and equipment should be validated.
• For all cleaning processes an assessment should be performed to determine the variable factors which influence cleaning effectiveness and performance, e.g. operators, the level of detail in procedures such as rinsing times etc. If variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies.
ANNEX 15 – CV 10.6

• Limits for the carryover of product residues should be based on a toxicological evaluation\(^1\). The justification for the selected limits should be documented in a risk assessment which includes all the supporting references. Limits should be established for the removal of any cleaning agents used. Acceptance criteria should consider the potential cumulative effect of multiple items of equipment in the process equipment train.

  – Therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. A toxicological evaluation may therefore not be applicable in these circumstances.

  – If it is not feasible to test for specific product residues, other representative parameters may be selected, e.g. total organic carbon (TOC) and conductivity.

• \(^1\) EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities
ANNEX 15 – CV 10.7

- The risk presented by microbial and endotoxin contamination should be considered during the development of cleaning validation protocols.
ANNEX 15 – CV 10.8

• The influence of the time between manufacture and cleaning and the time between cleaning and use should be taken into account to define dirty and clean hold times for the cleaning process.
ANNEX 15 – CV 10.9

- Where campaign manufacture is carried out, the impact on the ease of cleaning at the end of the campaign should be considered and the maximum length of a campaign (in time and/or number of batches) should be the basis for cleaning validation exercises.
ANNEX 15 – CV 10.10

- Where a worst case product approach is used as a cleaning validation model, a scientific rationale should be provided for the selection of the worst case product and the impact of new products to the site assessed. Criteria for determining the worst case may include solubility, cleanability, toxicity and potency.
ANNEX 15 – CV 10.11

• Cleaning validation protocols should specify or reference the locations to be sampled, the rationale for the selection of these locations and define the acceptance criteria.
ANNEX 15 – CV 10.12

• Sampling should be carried out by swabbing and/or rinsing or by other means depending on the production equipment. The sampling materials and method should not influence the result. Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.
• The cleaning procedure should be performed an appropriate number of times based on a risk assessment and meet the acceptance criteria in order to prove that the cleaning method is validated.
ANNEX 15 – CV 10.14

- Where a cleaning process is ineffective or is not appropriate for some equipment, dedicated equipment or other appropriate measures should be used for each product as indicated in chapters 3 and 5 of EudraLex, Volume 4, Part I.
ANNEX 15 – CV 10.15

• Where manual cleaning of equipment is performed, it is especially important that the effectiveness of the manual process should be confirmed at a justified frequency.
• Cleaning Validation
  – Cleaning validation is documented evidence that an approved cleaning procedure will reproducibly remove the previous product or cleaning agents used in the equipment below the scientifically set maximum allowable carryover level.

• Cleaning verification
  – The gathering of evidence through chemical analysis after each batch/campaign to show that the residues of the previous product or cleaning agents have been reduced below the scientifically set maximum allowable carryover level.

• Worst Case
  – A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.
• Terapeutiske principper
  – Tidligere har rester af lægemiddelstoffer i et produkt været vurderet på baggrund af kriterier relateret til laveste terapeutiske dosis, en sikkerhedsfaktor på normalt 1/1000 og en højeste tilladte mængde på 10 ppm. Denne værdi er rent empirisk og har i praksis været gældende for enhver fremmed forurening
• Toksikologiske principper – kendte stoffer
  – Hvor der ikke er tale om lægemiddelstoffer, dvs. hvor der ikke findes en laveste terapeutisk dosis, har tilsvarende vurderinger fundet sted på baggrund af toksikologiske data, typisk akut toksicitet i form af LD50.

  – Da akut toksicitet ofte ikke giver det fulde billede af betydningen af kontaminering, især ved langtidseksponering, benyttes
    • NOAEL (No Observed Adverse Effect Level)
    • ADI (Acceptable Daily Intake – ses nogen gange at betyde Anbefalet Dagligt Indtag, på engelsk RDI, Recommended Daily Intake. Dette er dog misvisende i denne sammenhæng)
    • ADE (Acceptable Daily Exposure)

BEREGNINGSPRINCIPPER ≤ 2014

• Toksikologiske principper – ukendte stoffer
  – Ved ukendte eller potentielt kræftfremkaldende stoffer kan lignende
    principper, der er beskrevet i ICH Q3x guidelines, benyttes. De omfatter
    primært syntese- og/eller nedbrydningsrester fra API’er, og er yderlige
    præciseret i Guideline on the Limits of Genotoxic Impurities,
    (EMEA/CHMP/QWP/251344/2006) med tilhørende Question & Answers
    on the CHMP Guideline on the Limits of Genotoxic Impurities
    • Disse dokumenter er fra henholdsvis 2006 og 2007 (rev 3/2010), og heri beskrives en
      generelt acceptabel tilgang gennem begrebet ”Threshold of Toxicological Concern”
      (TTC). En TTC-værdi på højst 1,5 µg/dag af en genotoxisk urenhed vurderes at være
      associeret med en acceptabel risiko (excess cancer risk of <1 in 100,000 over a
      lifetime) for de fleste farmaceutiske stoffer. Fra denne TTC-værdi/grænse kan der
      beregnes et acceptkriterium for de aktuelle stoffer baseret på forventet daglig dosis.
    • Hvis niveauet af f.eks. en mutagen urenhed er mindre en TTC-værdien, dvs. svarende
      til en klinisk dosis på ≤1.5 µg/dag, er det ikke nødvendigt at gennemføre yderligere
      ALARP-betragtninger (As low as Reasonably Possible) med mindre stoftets struktur
      godtgører, at grænseværdien skal nedsættes yderligere, f.eks. N-nitroso, aflatoxin-
      lignende eller azoxy-stoffer (Q&A dok.).
BEREGNINGSPRINCIPPER > 2014

• De toksikologiske principper er i perioden frem til 2012 blevet udviklet yderligere, især via ICH (The International Conference on Harmonisation), og senest er de gjort gældende i 2015 via EMA (European Medicines Agency) i Eudralex Vol. 4. Tilsvarende er gjort gældende i USA via FDA (Food and Drug Administration), men hele området er endnu ikke fuldt udviklet, og der efterlades mange åbne spørgsmål.

• Den væsentligste ændring i lovgivningen er, at der nu fokuseres på risikostyring – også når det drejer sig om cleaning validation. Begrebet PDE (Permissible Daily Exposure) er introduceret tillige med anvisninger om hvorledes værdien skal beregnes.

<table>
<thead>
<tr>
<th>Eudralex Vol. 4 Annex 15 Qualification and Validation</th>
<th>n/a</th>
<th>30-03-2015</th>
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<td>Deadline for coming into operation: 01-12-2015</td>
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| Deadline for coming into effect: 01-06-2015 |                                      |            |

| Eudralex Vol. 4 Part 1 – Chapter 3: Premises and Equipment | n/a | 13-08-2014 |
| Deadline for coming into operation: 01-03-2015 |                                      |            |
| However, the toxicological evaluation mentioned in section 6 is to be carried out from 1 June 2015 onwards for any medicinal product newly introduced into shared manufacturing facilities |     |            |

| Eudralex Vol. 4 Part 1 – Chapter 5: Production | n/a | 13-08-2014 |
| Deadline for coming into operation: 1 March 2015. |                                      |            |
| However, the toxicological evaluation mentioned in section 20 has to be carried out; From 1 June 2015 onwards for any medicinal product newly introduced into shared manufacturing facilities |     |            |
BEREGNINGSPRINCIPPER > 2014

PDE = NOAEL x Weight Adjustment
F1 x F2 x F3 x F4 x F5

- 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 an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.
- The use of additional modifying factors to address residual uncertainties not covered by the above factors may be accepted provided they are well supported with literature data and an adequate discussion is provided to support their use e.g. lack of data for reproductive and developmental toxicity
Beregningsprincipper > 2014

- Filosofien virker umiddelbart uoverskuelig, men i praksis
  - er det reelt tidligere praksis, der nu er nedskrevet og blevet til det man skal: arbejde ud fra kendskab til og styring af risici – risiko er i denne sammenhæng risiko for patienten
  - skal man begrunde sine valg med videnskabeligt funderede og dokumenterede rationaler.

- Også i den oprindelige terapeutisk funderede beregning af tilladt forurening har man opereret med reduktionsfaktorer f.eks. ved, men ikke begrænset til, hvis produktet skulle gives til børn, hvis stoffet var erkendt teratogent eller mutagen, hvis det var til særlig land behandlingstid etc.
OPERATIONELT

• I mange tilfælde er det vanskeligt for ikke-toxikologer at fastsætte de reducerende faktorer F1-F5 i PDE-beregningen, og derfor er det ofte påkrævet at rådføre sig med toxikologer og i fællesskab nå frem til den endelige PDE-værdi. Dette gælder især, hvor der måtte være forhold omkring et stof, der ikke er dækket af faktorerne F1-F5.

• Der hvor den nye praksis bliver mest uoverskuelig er i de tilfælde, hvor PDE bliver meget høj, fordi der reelt er tale om et relativt ufarligt stof.
  – Her anviser lovgivningen ingen regler, men det vil i henhold til god skik være rimeligt at kigge på de tidligere beregningsprincipper udfra terapeutisk dosis, og ikke mindst stadig sætte en grænse på 10 ppm for enhver fremmed forurening. Dette i sagens natur uanset om en toksikologisk beregning kunne tillade en større forurening.

• Endelig anviser lovgivningen tillige, at processens kapabilitet skal inddrages i fastsættelsen af acceptkriterier og/eller grænser for rengøringen.
  – Dette er til tider en udfordrende krav, idet der især i tidlige udviklingstrim, ikke forefindes mange relevante data. Kravet kan her forstås som, at hvis den relevante analysemetode typisk finder X til 2X ppm, og det aktuelt beregnede acceptkriterie resulterer i en grænse på 10X ppm, så vil en grænse på f.eks. 3 ppm give mening.
• Et eksempel fra det virkelige liv - Derived PDE

• PDE = NOAEL x Weight Adjustment / F1 x F2 x F3 x F4 x F5

• NOAEL (teratogen) = 1 mg/kg/day (studies described in appendix to this document)

• F1 = 5 to account for extrapolation from rats to humans
• F2 = 10 to account for differences between individual humans
• F3 = 1 because long duration of treatment
• F4 = 10 because teratogenic effect was reported
• F5 = 1 because a NOAEL was established

• The modifying factors (safety factors, F1-F5) are the ones used in the Pharmacopeial Forum (1989) and Environmental Health Criteria 170, WHO, Geneva, 1994)

• PDE = 1 mg/kg/day x 50 kg / 5 x 10 x 1 x 10 x 1 = 0.5 mg/day
• Acceptkriterierne for rengøring skal efter nutidige regler og retningslinier som tidligere nævnt baseres på toxikologisk funderede PDE-værdier. Dette betyder dog ikke, at de hidtidige principper skal forkastes, især ikke, nær der er tale om vidtgående tolerable stoffer, dvs. stoffer der har en forholdsvis høj PDE-værdi, som det er tilfældet med de aktuelle APIer.

• Når acceptkriterierne for den enkelte swaberprøve beregnes ud fra de forskellige principper fås følgende værdier, der er gældende for begge stoffer:
  – **PDE**
    • 0,5 mg/dag for THC
    • 0,5 mg/dag for CBD
    • 0,5 mg/dag for hver
  – **Terapeutisk**
    • 2,7 mg for THC
    • 2,5 mg for CBD
    • 2,5 mg for hver
  – **≤ 10 ppm**
    • I alt fremmed substans
    • SAMLET = I ALT!
Generelle formler for MACO eller MAC\textsubscript{APF}

Generelt anvendes følgende formel til beregning af maksimalt tilladt overført kontaminering:

\[
MAC_{APF} = \frac{X_{API} \times SBS_B}{WSD_B \times DD_B}
\]

hvor

\[X_{API} = PDE = NOAEL \times Aw / F1 \times F2 \times F3 \times F4 \times F5\]

ved nutidige beregninger

eller

\[X_{API} = ADI_{API} = NOAEL_{API} \times AAW \times SF\]

ved tidligere toxikologiske beregninger

eller

\[X_{API} = ADI_{API} = STD_A \times SF\]

ved tidligere farmakologiske beregninger

\[\begin{array}{ll}
S_{DA} & = \text{Mindste terapeutiske dosis, aktuelle produkt} \\
S_{BS} & = \text{Mindeste batchværdie, efterfølgende produkt} \\
SF & = \text{Stikprøvedosifaktor, normalt 1/1.000} \\
W_{SD} & = \text{Vægt af enenlæget (tabletvægt), efterfølgende produkt} \\
D_{DD} & = \text{Antal enekilder per dag, efterfølgende produkt} \\
ADI & = \text{Acceptabel daglig dosis} \\
NOAEL & = \text{Den dosis, hvor der netop ikke ses bivirkninger} \\
AAW & = \text{Gemensamt vekselvægt, normalt 70 kg} \\
PDE & = \text{Tilladt daglig eksponering} \\
AW & = \text{Vekselvægt i PDE-beregninger, typisk 30 kg}
\end{array}\]
Generelle formler for individuelle MAC-opgørelser
MAC fordelt på produktberørt udstyrareaal

\[ MAC_{PSA} = \frac{MAC_{Aa} \times 1000 \text{ (kg/mg)}}{PSA} \text{ mg/cm}^2 \]

MAC for den enkelte swab-test

\[ MAC_{Swab} = MAC_{PSA} \times SSA \text{ mg/cm}^2 \]

PSA = Udstyrstogets samlede areal
SSA = Swabets overladsareal
ADS = Mængde af ekstraktsionsvæske
OPERATIONELT – HVAD SÅ?

- Når aktuelt beregnede $\text{MAC}_{\text{API}}$-værdier sammenholdes:

- PDE-baseret beregning giver i alle tilfælde de højeste værdier
  - Dette beregningsprincip kan ikke benyttes, da MAC overstiger det højst tilladelige jf. 10 ppm-kriteriet

- Terapeutisk baseret beregning giver i alle tilfælde de laveste værdier
  - Dette beregningsprincip er anvendeligt, men i visse udstyrstog er acceptkriteriet lavere end analysemetodens LOQ. Dette giver anledning til formelle problemer i relation til godkendelse af swab-prøver.
  - Endvidere giver dette beregningsprincip meget lave acceptkriterier i forhold til det PDE-baserede beregningsprincip. Der er derfor intet toksikologisk problem forbundet med ikke at sætte så lave acceptkriterier

- Max 10 ppm-baseret beregning giver værdier i mellem
  - Dette beregningsprincip skal forstås som de acceptkriterier, der giver den maksimalt tilladte fremmede forurening.
  - Acceptkriterierne gælder for summen af de to APIer og er langt under det PDE-baserede niveau, hvorføl den ud fra en toksikologisk vurdering ikke udgør et problem

- *X* -baseret beregning giver værdier mellem Max 10 ppm og PDE
  - Dette beregningsprincip viser, at kun det PDE-baserede beregningsprincip medfører højere overført forurening, dvs. kun ved brug af det PDE-baserede princip, kan der potentielt tænkes en forurening, der vil kunne spores i en blodprøve.
OPERATIONELT – HVAD SÅ?

• I praksis skal acceptkriterierne også tilpasses processens kapabilitet, dvs. aktuelle swab-værdier skal inddrages i fastsættelsen af acceptkriterier og/eller grænser for rengøringen. Eftersom der endnu ikke findes erfaringer med rengøring og swab-testning efter produkter i projekt XYZ, kan denne inddragelse ikke ske.

  – Indtil erfaring er tilgængelig må acceptkriterier iht. ≤ 10 ppm princippet anvendes
HPLC VS TOC

• HPLC
  – Foretrukken – fordi den direkte bestemmer API
    • Men mindre god ifbm nedbrydningsprodukter
    • Pas på standtid mellem vask/swab og mellem swab/analyse
  – Kan være meget robust overfor forurening – og kan være ekstremt følsom
  – Swab-medier med opløsningsmidler kan anvendes

• TOC/NVOC(NPOC)
  – Pas på definitioner – er egentlig VOC + NVOC. I praksis NVOc!
  – Især god ifbm nedbrydningsprodukter eller hurtigt nedbrydende stoffer
  – Tager ALT TOC med, dvs. TOC-mængde = API-mængde
    • Følsom overfor forurening fra alt muligt
    • Swab-medier med opløsningsmidler kan IKKE anvendes