



Leachables & Extractables – The Toxicologist’s Perspective

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Leachables & Extractables – The Toxicologist’s Perspective

Background

- § An essential, critical component of the registration package for a parenteral product
- § Basic premise is that the risk to humans resulting from unintentional exposure to chemicals that migrate into drug product from packaging must be assessed
- § Any surface the drug comes in contact with is a source for potential chemical contamination and as such is subject to leachable and extractable studies
 - § Vials, rubber stoppers, inhalation delivery devices
 - § For a recent dry powder inhaler project, assessments were performed on chemicals originating from blister packaging that held the drug, and components of the plastic delivery device including the mouthpiece

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Background

- § There are currently no regulatory guidelines in place for assessing the risk of leachables and extractables (i.e. how does one do this?)
 - § Comprehensive assessments are performed for each chemical
 - § Assessments are based upon available animal and human toxicology data for the chemical, as well as analysis of the chemical structure (i.e. DEREK database)
 - § Average assessment time is 2 weeks for each chemical per toxicologist assigned
- § The PQRI recommendations may ease this burden, by establishing a threshold concentration below which no assessment is needed

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Background

- § The leachable/extractable work, and the risk assessment procedures are best performed on packaging components that are as close to, if not the exact ones intended for the market
 - § Substantial changes negate the assessment since the impurity profile may change
 - § Early involvement of the toxicologist from the experimental planning stage through the data collection greatly facilitates arriving at a timely and successful assessment of these chemical impurities
 - § Information regarding constituents/chemical make up of packaging components should be obtained from the manufacturer if available
 - § While such information is getting easier to obtain, continued improvement in communication and information exchange would be desirable

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Background

- § Assessment may yield issues that may guide subsequent material selection for packaging
 - § Some ink dyes contain PNAs such as benzo(a)pyrene, a known carcinogen
 - § Phthalate leachables recently detected from barrels used to transport finished drug product from manufacturing facilities
 - § Rubber stopper for intravenous product yielded latex leachable resulting in a packaging change

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Extractables

- § Extractable data are generated prior to determining the leachable profile
- § From a toxicology perspective, formal reportable risk assessments are typically not performed on extractables
 - § Not representative of “real life” circumstances
 - § Aggressive chemical manipulation of the packaging (e.g. strong solvents) is utilized to determine what chemicals might possibly leach into the drug (i.e. the extractables), not what actually makes it into the drug under more realistic circumstances (i.e. the leachables)
 - § A “bad actor” identified as an extractable may not even be a leachable!

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Extractables

- § Typically, the leachables will be a subset of the extractables
- § Toxicologist may run DEREK analyses on extractables, and perform a cursory high level look at relevant safety data for each extractable
 - § This gives the toxicologist a heads - up regarding potential issues that may arise when leachable data are subsequently generated
 - § Allows identification of a potentially problematic chemical early on when it is easier to make changes to the container closure system, or time to work with supplier to mitigate the problem
- § Knowing number of extractables helps toxicologist plan for proper resource deployment that will be needed for leachable risk assessment work

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Risk Assessing Leachables – What We Need

- § **Dose** – Under conditions of maximum daily use of the drug, how much of a total daily dose of the leachable will be co-administered to humans?
 - § PPM must be converted into dose, or it has little use to a toxicologist performing a risk assessment
 - § If Drug A is given at 1 gram/day, the dose of a leachable present @ 1 ppm is 1 µg
 - § If Drug B is given at 10 mg/day, the dose of a leachable present @ 100 ppm is also 1 µg

"Alle Ding' sind Gift und nichts ohn' Gift; allein die Dosis macht, dass ein Ding kein Gift ist."
 PARACELSUS (The "Father" of Toxicology)

"All things are poison and nothing is without poison, only the dose permits something not to be poisonous"

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Risk Assessing Leachables – What We Need

- § **Duration** – How long will the patient be exposed to the leachable? Chronic, daily exposure to a potential toxin always carries a higher theoretical risk of eliciting an adverse effect than short-term exposure
 - § Greater scrutiny of safety data supporting a leachable will be paid to those in chronic use drugs
- § **Route of Administration** – Can affect the toxicological profile of any toxin
 - § If not absorbed, may not be toxic via the oral route, but very toxic intravenously!
 - § Different metabolites can form after giving an agent by different routes (i.e. oral versus intravenous)

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Risk Assessing Leachables – What We Need

- § **Patient population** – Are volunteers or patients with the disease receiving the drug containing leachable(s); health status can influence the risk assessment
- § **Indication** – What is being treated by the drug has great influence on a risk assessment; greater risk is tolerated if the drug is to treat a life-threatening illness!
- § **“Special” populations** – factors such as a potential pediatric indication, administration to an elderly population, need to be understood to better assess potential risk
- § **Women of Child Bearing Potential** – Reproductive toxicology data for the leachable would be needed to support safety if WOCBP are to be dosed with the drug

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Standard Layout of Data For A Risk Assessment

- § DEREK (if needed)
- § Genetic toxicology
- § Acute toxicity
- § Subchronic toxicity
- § Chronic toxicity
- § Carcinogenicity
- § Reproductive toxicology
- § Human toxicity data
- § Special populations (e.g. pediatrics)
- § Regulatory guidance information (e.g. OSHA, EPA, WHO)


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Pfizer Case Studies – The Challenges


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Case 1 - Inhaled Dry Powder Leachable Project

- § No regulatory guidelines available
- § Details on constituents/components of inhaled delivery device and drug blister pack not available from manufacturers
- § After developing in - house risk assessment strategy and procedures, a total of 28 leachables from the drug blister packs were risk assessed for the US and European filing
- § Identifying components was resource intensive, and there was no assurance that what was identified would not be problematic
- § We received no comments from regulators concerning the assessments





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Case 2 – A Pulmonary Delivery Device

- § Worked with a supplier who wants to, and has established a scientific rapport with the pharmaceutical industry
- § Material names and CAS numbers of component materials were made available
- § They had ISO testing already completed to confirm materials were acceptable
- § Overall, we therefore knew the constituents and their basic safety test results
- § Proceeded with leachable and extractable work with high degree of confidence that encountering a problematic chemical would be negligible
- § Analytical chemical analyses were simplified with advance knowledge of constituent identification



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Case 3 – An Ocular Delivery Device

- § Component of device had sulfur - cured rubber (elastomer)
 - § Mercaptobenzothiazole (MBT) is a common accelerant utilized in the sulfur curing process
 - § MBT is a compound of concern due to suspected carcinogenicity issues
- § A confidentiality agreement was developed with the manufacturer
- § Manufacturer did provide a list of constituents and CAS numbers!
- § Would not reveal details of what accelerant they utilized in their manufacturing process except it was not MBT
 - § A proprietary procedure they were not willing to disclose?

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Case 4 – A Pulmonary Delivery Device

- § Pharmaceutical Sciences identified materials well suited for use in a particular device
- § A confidentiality agreement was developed with the manufacturer
- § Company expressed no interest in involvement in the project whatsoever
 - § Low return on investment?
 - § Perceived liability issues?
- § We must do controlled extraction studies with no advanced knowledge of components whatsoever
- § Loss of time if a problematic constituent is identified

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