RISK IDENTIFICATION FOR MANUFACTURE IN SHARED FACILITIES

Basic Principles of API Risk Assessment

Prof. Andrew Bartholomaeus
School of Pharmacy, University of Canberra
Therapeutic Research Centre, School of Medicine, University of Queensland
CEO, BartCrofts Scientific Services Pty Ltd

Email; BartCrofts@gmail.com

Synopsis

- A general overview of the process and potential complexity, More detail in the toxicology stream tomorrow
- Final EMA Guidance - EMA/CHMP/SWP169430/2012 . Effective 20 November 2014
- Compliance will require an expert review
  - The review is potentially substantial and involved
  - Required for each Active Pharmaceutical Ingredient (API) **& product sequence**
  - Must be signed off by an "expert" and include their CV
- For **innovator Companies** data requirements and assessment not onerous – drawn from preclinical and early phase clinical datasets
- For **generic companies** there are some real challenges & substantial costs involved
- Dedicated facilities for high risk products unavoidable and reasonable
  - Potent Allergens
  - Potent Genotoxic actives
- A number of aspects of the Guidance are peculiar (or just wrong) and disproportionate to risk – eg;
  - Derivation of PDE based on life time exposure
  - Incorrect description of NOAEL determination
  - Conflation of Risk Assessment and Risk Management

Fairly simple decision tree

1. Is the active highly allergenic or sensitising
    o Unless a threshold has been identified
    o Requires a Dedicated manufacturing facility
2. Is the active Genotoxic
    o Yes Go to 3
    o No Go to 4
3. For genotoxic substances can a threshold be Identified
    1. Yes – Go to 4 (calculate PDE)
    2. No – Apply a threshold of toxicological concern (TTC) of 1.5 μg per person per day
4. For non genotoxic actives calculate PDE (&/or consider TTC)
    1. TTC for non genotoxic chemicals is 1.5 μg per kg bw/day
        1. Excluding high potency bioactives such as organophosphate AChE inhibitors for example
    2. Non-genotoxic TTC not expressly permitted in guidance however
    3. May not be appropriate for very high potency drugs. Eg digoxin

In a nutshell

1. ## Calculate the Permissible Daily Exposure (PDE)
   1. ie. how much of an API, as a contaminant in a subsequent product in the manufacturing sequence, could be administered to a person every day for a lifetime without appreciable risk of adverse effects.
   2. ? Are there different PDEs or different subpopulations
2. ## Determine likely carry-over between batches
   1. Either estimate a worst case carryover or measure the amount of the that API that remains in the production process line following cleaning and could find its way into subsequent products.
3. ## Assess Risk to patients of the contaminated product
   1. EITHER daily exposure is below the PDE for everyone in the population or it is below the PDE for the most sensitive patient group using the contaminated product.
   2. eg no value in using a PDE derived from developmental studies for a drug that will never be given to pregnant women because of the therapeutic indication or which is itself a strong teratogen – eg retinoic acid

The New Process

- "Evidence based",
  - A refinement certainly but many arbitrary non science based requirements remain.
- But, Replaces requirement for
  - max 10 ppm cross contamination or
  - $1/1000^{th}$ of clinical dose, or
  - dedicated facility
- Hazard Characterisation is based on donating product, you will need;
  - An Human Health Risk Assessment (HHRA) for every active (API) in every product you manufacture
    - ***Requires Expert Certification***
- Exposure Assessment is based on both donating and receiving products
  - ie product sequence specific

Hazard Characterisation

- Hazard Characterisation is based on the API in the donating product, you will need;
  - An Human Health Risk Assessment (HHRA) for every API in every product you manufacture
    - The PDE is specific to the active, not the product it is in or the process of manufacture, so once determined there will be no need to repeat this specific part of the risk assessment.
    - A PDE determined for one route of administration (eg oral) may need adjustment for another route of administration (eg intravenous, inhalation or dermal)
    - Requires Certification by a Demonstrated Expert (toxicologist)
    - Determination of the PDE is likely to require an external expert for most generic producers
      - **"Following an expert review,** …. provide a **discussion with respect to the critical endpoints of concern** and ..**rationale for** the …..**dose** …**used** in the **derivation of the PDE**. The pivotal ….studies .. for the …PDE should be **sourced to the original reference** and **reviewed** regarding their quality (**study design, description of finding, accuracy of the report etc**.). ……..**provide a clear rationale regarding the adjustment factors that were applied** in deriving the PDE."
  - **Human data will yield higher PDEs than animal data due to the way uncertainty/ adjustment factors are applied**

Exposure Assessment

- **Exposure Assessment based on receiving Product**
  - Should be within the capacity of most QA/QC sections of generic manufacturers once a PDE has been calculated
- **you will need to;**
  - consider both the donating and receiving products to determine the potential residual levels of active following clean-up of the equipment
    - How much material could remain from the preceding product
    - For tablets and capsules is there a substantial size differential
      - Eg if second tablet >> size of first then higher proportion of an active dose could plausibly be contained in the receiving product
      - If second tablet << than size of first then only a very small proportion of an active dose could plausibly transfer to second product
  - Determine quantity and distribution of likely carry over
    - How is it distributed – ie lumpy, an even continuous contamination, or starting higher then tailing off over the course of the batch process
    - Potential contamination from broader manufacturing environment
      - Clothing, air, other ?
  - Consider the target population sensitivities for the receiving product or use PDE for the most sensitive target population to the range of critical effects identified, ie who is being exposed to the receiving product, eg
    - Children
    - Women of child bearing age
    - Severely debilitated, immunocompromised, liver or renal function compromised etc individuals
    - Product (donating and receiving) and process specific
    - This aspect will be within the capabilities of the QC/QA staff within most facilities

Risk Assessment

General Components of Risk Assessment

Regardless of the Regulatory Regime there are common components of different nature

- Science – substance specific, requires specific expertise and data
  - What are the potential adverse effects in humans
    - Clinical Trials
    - Animal Studies
    - *In vitro* and *in silico* data
  - How much is "safe"
- Policy - general and specific – dictated by regulators
  - Uncertainty/Adjustment Factors
  - Threshold paradigm
  - Model exposure periods (acute, sub acute, chronic)
  - Degree of Conservatism
- QC/QA/GMP – regulatory and company – dictated by the regulator and product stewardship related requirements
  - Cleaning procedures, validation, frequency, thoroughness etc
  - Determination of residues, validation
  - Pattern of release/contamination in subsequent batch(es)
- Process- Regulatory - dictated
  - Documentation
  - Validation
- Procedural – management – business in the real world
  - Manufacturing sequence
  - Cost containment
  - Profitability, economic viability

Determination of the PDE

- ## PDE = Permitted Daily Exposure (ADI, TDI)
  - Amount that can be consumed (dosed) daily for a lifetime without appreciable risk
  - This is an irrational standard for batch to batch contamination but is the requirement nonetheless
  - In practice, for most APIs the **pivotal** critical effect will not require lifetime exposure to be manifest
    - eg teratogenesis, genotoxicity, pharmacodynamic effects
- ## Perform a standard step Human Health Risk Assessment
  - Hazard Identification
  - Hazard Characterisation
  - Exposure identification
  - Exposure Characterisation
  - Risk Characterisation

Stepping through the process

1. IDENTIFY HAZARDS
2. DETERMINE THE CRITICAL EFFECT(S)
3. DETERMINE THE POINT OF DEPARTURE POD
4. APPLY UNCERTAINTY FACTORS
5. CALCULATE PDE
6. APPLY "REALITY CHECKS"
7. ASSESS EXPOSURE LEVELS
8. COMPLETE RISK CHARACTERISATION

HHRA – Step 1 Hazard Identification

- **Gather all data** potentially relevant to the toxicology assessment of the substance of interest.
  - Requires a formal literature search strategy if based on published sources.
- **Screen data** for quality and reliability (if possible).
  - **GLP** status of the test facility
  - **Test Guideline Compliance**
  - **Transparency**, quality and detail of data and method presentation
  - **Suitability of study design**
- **Identify potentially treatment related effects** in each study, considering
  - **Dose response** in terms of incidence and severity of each effect
  - **Magnitude of the apparent effect** compared to background variation, using
    - **Concurrent control**(s) in the specific study
    - **Baseline values** for individual animals/subjects determined prior to commencement of dosing
    - **Historical controls** for the specific strain & source of test species
    - **Species variation data** more broadly – for rare endpoints
  - **Concordance** of the observation with correlating parameters
  - **Statistical significance**

Step 1 - Sources of Data

- **European Medicines Agency**
  - EPAR (European Public Assessment Reports - Summary of submission and evaluation)
    - http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124
  - Clinical reports – from mid 2016
- **US FDA**
  - Drugs@FDA
    - http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
- **Australian TGA**
  - Product Information Documents
    - http://search-au.funnelback.com/s/search.html?collection=tga-artg
  - AusPARs (Australian Public Assessment Reports)
    - https://www.tga.gov.au/browse-auspars-active-ingredient
  - Prescribing Medicine in Pregnancy
    - http://www.tga.gov.au/prescribing-medicines-pregnancy-database
- **NIH**
  - TOXNET (collection of databases including DART, TOXLINE, HSDB)
    - http://toxnet.nlm.nih.gov/
  - DailyMed
    - http://dailymed.nlm.nih.gov/dailymed/index.cfm
    - HSDB
- **For Vitamins and Minerals use Nutrient Reference Values, Upper Levels**
  - Eg US IOM - http://ods.od.nih.gov/Health_Information/Dietary_Reference_Intakes.aspx
  - Australian NHMRC - https://www.nrv.gov.au/
- **Abstracting data bases, eg MEDLINE, PUBMED**

Hazard Identification Cont

- **Assess the toxicological significance** of the observed effects *to the model* (or test population) in terms of
  - The **biology of the model**/test species/sub population considering
    - **Species specific ADME** of the compound (or any potential genetic PK differences in the test population)
    - **Presence or absence of specific targets** (organs/tissues/biochemical pathways)
  - **Toxicology**, differentiating between adaptive responses and adverse effects, considering
    - **reversibility** of the effect
    - **pathological significance** of the endpoint in terms of normal biological and physiological function, longevity of the test species
    - **Time of onset** in comparison to the life span of the test animal
    - **Progression** of the severity &/or incidence of the effect over time
    - **Species** specificity or cross species concordance of effect
    - **Primary or Secondary** nature of the effect
    - **Mode of Action** leading to the effect.
  - **Statistics**
    - **Differentiate** between random statistical significance due to multiple comparisons from true effects based on a consideration of;
      - **Concordance** with correlating parameters
      - **Consistency across studies** in the same model/species/test population
      - **Consistency across species**/models/test populations
      - **Nature of the dose response** in terms of incidence and severity
- Consider the **relevance of the test system**, study design, animal model or other data generation technique, to the population potentially at risk of exposure to the substance.
  - **Mode of action**
  - **Comparative biology, anatomy and behaviour** between test species and man
- **Identify the population potentially at risk** from those effects (gender, age group, life stages such as pregnancy, lactation).
- **Distinguish between adaptive and adverse effects**

HHRA Step 2 – Determine adversity
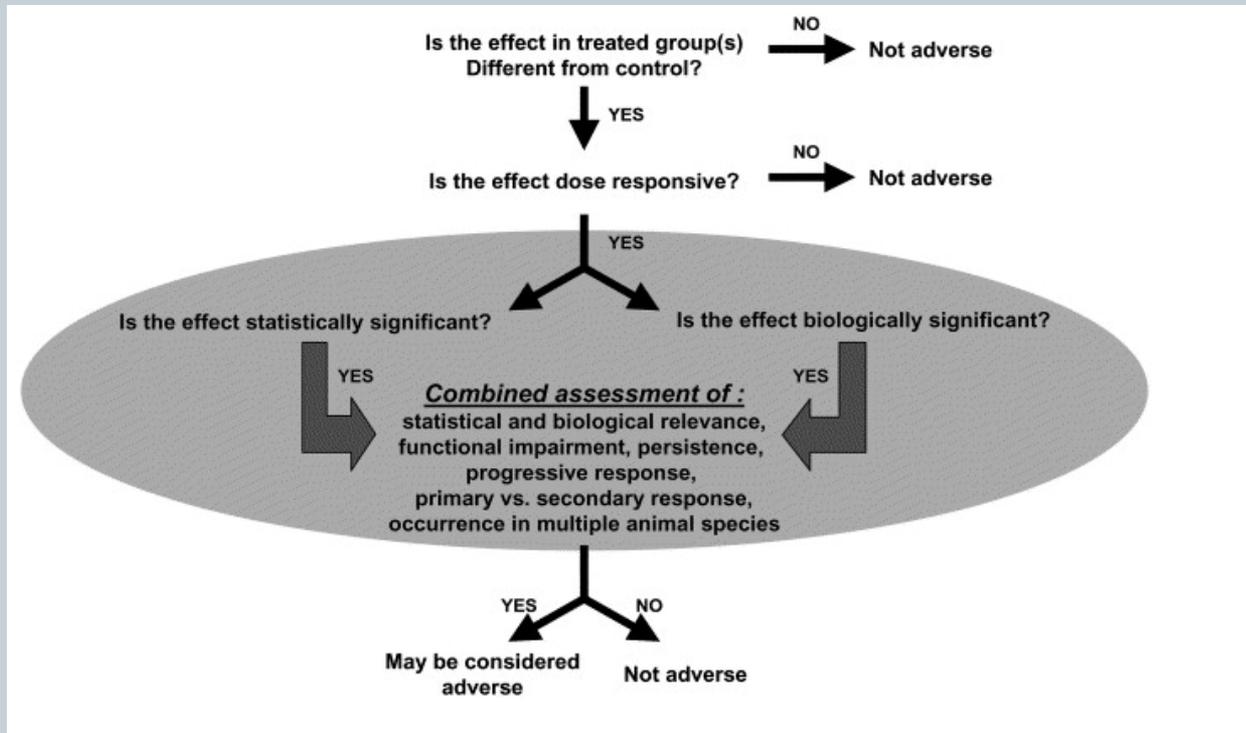
Approach to classifying toxicology study results as adverse or non-adverse (modified from Lewis et al., 2002 by Dorato and Englehardt 2005

HHRA Step 3 identify the Point of Departure

- From the list of adverse effects across all studies
  - Identify the effect that occurs at the lowest dose in the most sensitive species LOAEL– **that is relevant to humans**
  - Identify the highest dose, below the lowest LOAEL, at which the effect was not seen in that species
  - This is the overall NOAEL –or Point of Departure (POD) and is the dose that will be used to calculate the PDE

HHRA – Step 4 apply uncertainty/ Adjustment factors – A Dark and Arcane Art

- Uncertainty (adjustment - AF) factors are intended to compensate for the nature and potential magnitude of identified uncertainties

- **The application of UFs is the largest single determinant of the PDE and can have a large impact on permitted production practices ($$$$$) and internal processes**

- Sounds scientific but in reality is arbitrary and primarily policy based.

- **EXPERT JUDGEMENT + SOLID DATA** can however moderate UFs downwards (ie increase PDE)

Step 5 Calculate the PDE

- **If the API has adverse effects relevant to different sub-populations a series of PDEs may need to be established relevant to specific receiving products**

    - Women of child bearing age
        - (reproduction and developmental endpoints)
    - Patients with renal or liver failure –
        - kidney or liver as target organs
        - Effect on drugs eliminated by kidney or liver
    - Immunocompromised or severely debilitated patients
        - Immuno-suppressants
        - Genotoxins

Step 5 Calculate the PDE

- PDE is derived from the no-observed-**Adverse** effect level (NOAEL), or the lowest-observed-**Adverse** effect level (LOAEL) in the most relevant animal and/or human study as follows:

- $PDE = \dfrac{NOEL \times Weight\ Adjustment}{(F1 \times F2 \times F3 \times F4 \times F5)}$

F1 = An uncertainty factor to account for extrapolation between species (between 2 and 12)

        F1 = 5 for extrapolation from rats to humans

        F1 = 12 for extrapolation from mice to humans

        F1 = 2 for extrapolation from dogs to humans

        F1 = 2.5 for extrapolation from rabbits to humans

        F1 = 3 for extrapolation from monkeys to humans

        F1 = 10 for extrapolation from other animals to humans

F2 = A factor of 10 to account for variability between individuals

F3 = A variable factor to account for toxicity studies of short-term exposure

        F3 = 1 for studies > half a lifetime (1 yr rodents &rabbits;7 yrs cats, dogs & monkeys).

        F3 = 1 for reproductive studies in which the whole period of organogenesis is covered.

        F3 = 2 for a 6-month study in rodents, or a 3.5-year study in non-rodents.

        F3 = 5 for a 3-month study in rodents, or a 2-year study in non-rodents.

        F3 = 10 for studies of a shorter duration.

Adjustment factors Continued

F4 = A (very unscientific and arbitrary "feel good" or risk management) factor that may be applied in cases of severe toxicity, e.g., non-genotoxic carcinogenicity, neurotoxicity or teratogenicity. In studies of reproductive toxicity, the following factors are used:

      F4 = 1 for foetal toxicity associated with maternal toxicity

      F4 = 5 for f0etal toxicity without maternal toxicity

      F4 = 5 for a teratogenic effect with maternal toxicity

      F4 = 10 for a teratogenic effect without maternal toxicity

F5 = A variable factor that may be applied if the no-effect level (NOAEL) was not established

When only a LOAEL is available, a factor of up to 10 could be used depending on the severity (as opposed to type) of the toxicity. That is – how far away from a NOAEL is the LOAEL, close if toxicity is mild, more distant if severe. Requires a consideration of the dose response pattern.

The weight adjustment assumes an arbitrary adult human body weight for either sex of **50 kg**. This relatively low weight provides an additional safety factor against the standard weights of 60 kg or 70 kg that are often used in this type of calculation. It is recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the other built-in safety factors used to determine a PDE.

If the formulation is for paediatric use, use adjustment for an appropriately lower body weight

Step 6 Apply some cross checks - For potent pharmacological actives

- Check that the PDE is below the **highest** dose tested that is pharmacological **inefficacious** in HUMAN STUDIES
- For toxicologically benign actives a pharmacodynamic NOAEL based on *Clinical* studies can be used (eg macromolecules and peptides)
- **TOXICOLOGICALLY BENIGN =**
  - Not a Teratogen
  - Not a Reproductive toxin
  - Not a Genotoxin,
  - Not a Carcinogen, *AND*
  - No target organ effects at doses below adverse pharmacodynamic effects (ie adverse effects are principally due to excessive *PRIMARY* pharmacological effects)

Step 6 Continued
- Threshold of Toxicological Concern (TTC)

- Compare against TTC
- For genotoxins the TTC in the EMA guidance is 1.5 µg/person per day (some exceptions for potent genotoxins) – This is HIGHER than for general chemical TTC approaches because of batch to batch variation in level & presence.
- Not clear this approach is available for non genotoxins but worth including in any HHRA as a cross check and supporting consideration
  - Some high potency drugs and toxins are not suitable for this approach
- EC has generally accepted the principle across most other HHRA regulatory frameworks

Next Steps

- At this point a PDE has been established
- The next steps involve the exposure characterisation
  - A consideration of the potential carry over to receiving products
    - From production equipment
    - Manufacturing environment
    - Personal and material flow
    - Etc
  - A consideration of the dose volume of the receiving product
  - Calculation of maximum contamination per unit dose of the receiving product
- Lastly, is the potential level of contamination in the receiving product , and resulting patient intake, below the PDE for the most sensitive potential patient population of the receiving product

EU/EC TTC Considerations

- "The Scientific Committees accept in principle the division (of chemicals) into Class I and Class III" - ie toxicity classes I and II.
- For the lowest toxicity class
  - (Class I, 1800 μg/person/d corresponding to 30 μg/kg bw/d for substances without genotoxicity alerts), classification should be carefully considered and justified.
  - If classification in Class I cannot be justified the SCs recommend a general default value equivalent to Cramer Class III compounds (90 μg/person/d corresponding to 1.5 μg/kg bw/d **for substances without genotoxicity alerts**).
  - Some potent drugs are active at this level however
    - eg ethinyloestradiol has a lowest therapeutic dose of <0.4 μg/kg/day
- EXCLUDES
  - Anything that bioaccumulates
  - High potency - drugs, carcinogens
  - Allergens
  - Insoluble nanomaterials

Exsposure Assessment

- 3 general approaches
  - Quantitative
    - Use analytical QC approach to estimate actual cross contamination that occurs between batches of a product type (tablets, eye drops etc)
  - Qualitative
    - Estimate from experience etc the maximum residue that could go undetected in production equipment, or be deposited from protective clothing, under the conditions applicable to your facility
  - Reverse engineering
    - Work backwards – how much of product A would need to be in product b for that to result in an exposure greater than the PDE
      - Is that plausible/possible
      - eg is it impossible given the dose size of the follow on product
    - What processes are or could be in place to preclude that level of contamination
      - Would exceedance require a massive failure of the cleaning process
    - What evidence do you have to support your conclusions – ie how confident can you be in your conclusions
      - Are you looking through rose coloured glasses or being brutally realistic

Conclusions

1. **A FORMAL, EXPERT, HHRA WILL BE REQUIRED FOR EVERY ACTIVE INGREDIENT** used within a facility UNLESS it is produced in a dedicated facility that produces no products containing other actives
2. For Generic manufacturers the data requirements and assessments may well be extensive, costly and possibly challenging, particularly for older actives.
3. Determination of PDEs is (mostly) a once off exercise for each active (with regular review to ensure new data has not emerged that would alter the PDE) however
   - Weight factor is determined by receiving product
   - Relevance of some endpoints determined by patient population of receiving product
4. Each new production sequence will require a (relatively simple) Risk assessment based on the receiving product
   - Carry over per unit dose
   - Doses per day
   - Comparison of subsequent intake per day against PDE
   - Patient population & relevance of specific toxicological endpoints

The literature search, data acquisition and HHRA may take considerable time

- The time requirements should be included in business plans
- So don't leave it to the last minute
- Some "off the Shelf" HHRAs are of poor quality and very simplistic.
  - OK for some low toxicity, low potency APIs but be cautious for APIs with high pharmacological potency and potential high toxicity.
- Regulatory acceptance of the "Off The Shelf" HHRAs is unknown and suspect.

- **More detail tomorrow**