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Application of Data from HTS Assays in Regulatory Decision-making

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Acceptance of HTS Assays for Regulatory Decisions

- Can data from HTS be used for making regulatory decisions?
  - If not, what information is required?
- What are the criteria for regulatory acceptance?
- What information must an HTS assay provide to be incorporated into regulatory policy?
- What types of QA/QC should be included in each experiment?
  - Concurrent negative controls
  - Historical controls
  - Benchmarks?
- Is there a current role in the regulatory decision making process for HTS assay results?

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Acceptance of HTS Assays for Regulatory Decisions

- **What are the regulatory purposes related to HTS?**
  - Prioritization for use in medium-throughput and traditional in life studies
  - As adjunct to current tests in regulatory decisions
  - Reduce, refine, replace animal tests for risk assessments.

  - The confidence/stringency of the regulatory criteria will vary with the intended use of the data.

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Acceptance of HTS Assays for Regulatory Decisions

- **Can data from HTS be used for making regulatory decisions?**
  - In the near future, it may aid in priority setting. At this time, the information is primarily limited to “hazard ID”, but not useful in risk assessment.
  - You can NOT use this information for making regulatory decisions at this time, or in the foreseeable future.

- **If not, what information is required?**
  - Adequate validation of tests, uncertainty analysis, sufficient predictive high-throughput ADME methods, dose-response information as may be obtained using medium-throughput methods.
  - It’s preferable to increase the number of assays that are run with each chemical/agent, so that the number of endpoint outputs are increased.

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Acceptance of HTS Assays for Regulatory Decisions

- **What are the criteria for regulatory acceptance?**
  - Relevant (fits into exposure-disease continuum)
  - Reliable (a workable assay)
  - Repeatable (consistent results within/among labs)
  - Recognized (acceptance by a large diverse audience)
  - Realistic (outcome used for decision-making).

  - The confidence/stringency of the criteria varies with the intended use of the data. (i.e., prioritization, regulation for commercial use, 3 R's)

  - There needs to be a clear articulation of what constitutes an appropriate application of a particular HTS assay, including limitations, uncertainties, etc.

  - The ICCVAM validation process could be used to aid in the effort to define criteria for regulatory acceptance

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Acceptance of HTS Assays for Regulatory Decisions

ICCVAM http://iccvam.niehs.nih.gov/docs/guidelines/validate.pdf, pg 22

- The method should have undergone independent scientific peer review by disinterested persons who are experts in the field, knowledgeable in the method, and financially unencumbered by the outcome of the evaluation.
- There should be a detailed protocol with standard operating procedures (SOPs), a list of operating characteristics, and criteria for judging test performance and results.
- Data generated by the method should adequately measure or predict the endpoint of interest and demonstrate a linkage between either the new test and an existing test, or the new test and effects in the target species.
- There should be adequate test data for chemicals and products representative of those administered by the regulatory program or agency and for which the test is proposed.
- The method should generate data useful for risk assessment purposes, i.e., for hazard identification, dose-response assessment, and/or exposure assessment. Such methods may be useful alone or as part of a battery or tiered approach.
- The specific strengths and limitations of the test must be clearly identified and described.
- The test method must be robust (relatively insensitive to minor changes in protocol) and transferable among properly equipped and staffed laboratories.
- The method should be time and cost effective.
- The method should be one that can be harmonized with similar testing requirements of other agencies and international groups.
- The method should be suitable for international acceptance.

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- **What information must an HTS assay provide to be incorporated into regulatory policy?**
  - **Need predictability of the assay for the endpoint(s) of interest.**
    - **Predictability must provide information on sensitivity and specificity for a well-characterized reference database of test agents.**
  - **Need procedures for interpretation of the data.**

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Acceptance of HTS Assays for Regulatory Decisions

- **What types of QA/QC should be included in each experiment?**
  - **Concurrent negative and positive controls**
  - **Historical control standards**
  - **Benchmark controls (based on similar chemical or physical properties, or on similar levels of biological activity.)**
- **For regulatory acceptance, probably need all of the above, and possibly more, depending on the application of the assay. For example: GLP, vehicle controls, independent review, repeatability in independent labs, increased replicates, historical control data on positive/negative controls.**
- **HTS initially may require more QA/QC because the methods are novel, and need to earn scientific confidence. In the future, the level of QA/QC may be reduced**

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- **Is there a current role in the regulatory decision making process for HTS assay results?**
  - **Not currently.**
  - **In the near term, there is potential for chemical grouping by assay results, and prioritization**

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Guidance and Oversight

- **What type of guidance and oversight would regulatory agencies want to have in place, for the data from HTS assays to be useful to them?**
  - There are two issues:
  - 1) how well does the method perform for its intended use
  - 2) use of these data within a specific regulatory construct.
    - The guidance would need to be different for these two purposes. For the second, this may be agency-specific or program-specific within an agency.
  - There may need to be an interim policy on guidance and oversight for these data
  - Guidance needs to be developed in accordance with the specific regulatory purpose (prioritization, regulation for commercial use, and animal replacement)

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Relevance and Reliability of HTS

- **Does the relevance and reliability of each HTS assay (in terms of being able to predict or relate to a possible toxic response) need to be characterized or would the pattern of responses among related HTS assays be sufficient for regulatory needs?**
  - **Need to characterize both individual assays and assays in combination (i.e., pattern)**
  - **Show the relevance of each assay to the whole.**
  - **Relevance to the predictive model that links HTS to the appropriate application endpoint, such as animal or human toxicity.**
  - **Pattern in relation to dose**

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Outreach Program

- **Do we need to develop an outreach program to bring understanding to regulatory agencies about the usefulness and applicability of HTS?**
  - **Yes.**
    - **Workshops and training will be needed for people within the regulatory agencies that will have to review and evaluate these data**

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Usefulness of New Technologies

- How are regulatory agencies dealing with other new technologies (e.g., microarray data) that could be applied to data collected from HTS assays?
- Are these data being used presently in regulatory decision making and if so how?
  - Genomic data is not being used as stand-alone, it is being considered with other available data

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Usefulness of New Technologies

- **If not, what is needed so HTS data can be useful?**
  - **There needs to be training opportunities for regulators for the data to be useful**

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Extrapolation

- If a chemical perturbs a key pathway resulting in a regulatory decision, can all the chemicals in the same chemical class be assumed to respond similarly?
  - Not necessarily. Must have ADME information for all compounds tested
  - Need to consider multiple pathways and dose-response information from HTS and medium-throughput

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Perturbation of One Step in a Pathway

- Can regulatory decisions be made on a chemical (or mixture) based on the perturbation of one step in a pathway, such as being a specific receptor agonist or antagonist, or would more information be necessary?
  - This information could conceivably be used to group a chemical with its mode of action, but should not be considered rigorous data
  - Use of this data may be very limited.

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Non-Toxic Compounds

- **When are regulatory decisions made that a specific class of compounds is considered to be non-toxic?**
  - **Not able to make a decision that a class of compounds is non-toxic, even with robust traditional toxicological data.**
  - **Agencies consider both toxicity and exposure, to make a decision about what level, if any, is considered acceptable risk for an intended use.**

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All models are wrong but some are useful

From: Box, G. E. P. (1979). Robustness in the strategy of scientific model building. In R. L. Launer, and G. N. Wilkinson, (eds.) Robustness in Statistics. New York: Academic Press