MASTER DI II LIVELLO
SCIENZE REGOLATORIE DEL FARMACO
AIFA – LA SAPIENZA

VALUTAZIONE DEGLI STUDI TOSSICOLOGICI DI UN DOSSIER DI REGISTRAZIONE

VALUTAZIONE TOSSICOLOGICA DELLE IMPUREZZE

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22 Marzo 2013

Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	X	Attualmente	Precedenti 2 anni	Da oltre 2 a 5 anni precedenti	Oltre 5 anni precedenti (facoltativo)
Interessi diretti:					
Impiego in una società	X				
Consulenza per una società	X				
Consulente strategico per una società	X				
Interessi finanziari	X				
Titolarità di un brevetto	X				
Interessi indiretti:					
Sperimentatore principale	X				
Sperimentatore	X				
Sovvenzioni o altri fondi finanziari	X				

* Laura Braghiroli, secondo il regolamento sul Conflitto di Interessi approvato dal CdA AIFA in data 26.01.2012 e pubblicato sulla Gazzetta Ufficiale del 20.03.2012 in accordo con la policy 0044 EMA/513078/2010 sulla gestione del conflitto di interessi dei membri dei Comitati Scientifici e degli esperti.

Per questo intervento non ricevo alcun compenso

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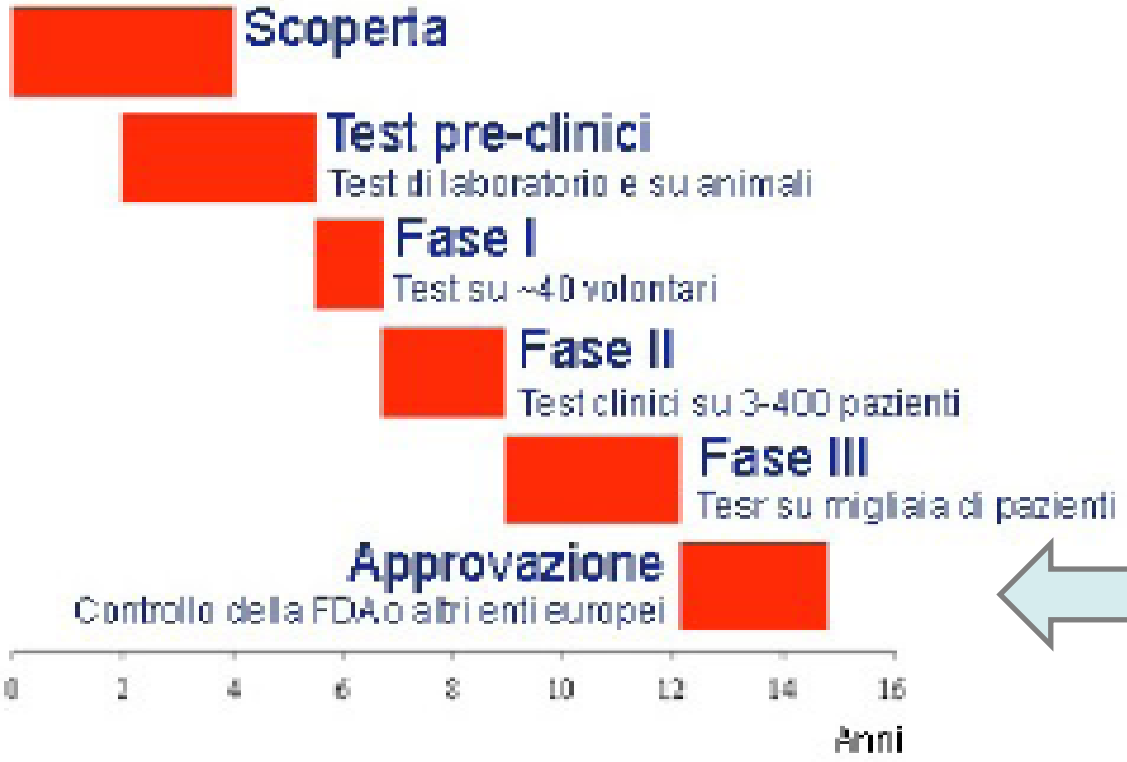
SVILUPPO DI UN FARMACO

Per ottenere l'autorizzazione all'immissione in commercio (AIC), un farmaco deve essere sottoposto ad una lunga sperimentazione atta a stabilirne la sicurezza e l'efficacia.



AIC

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SVILUPPO DI UN FARMACO
FASE PRECLINICA

STUDI DI EFFICACIA

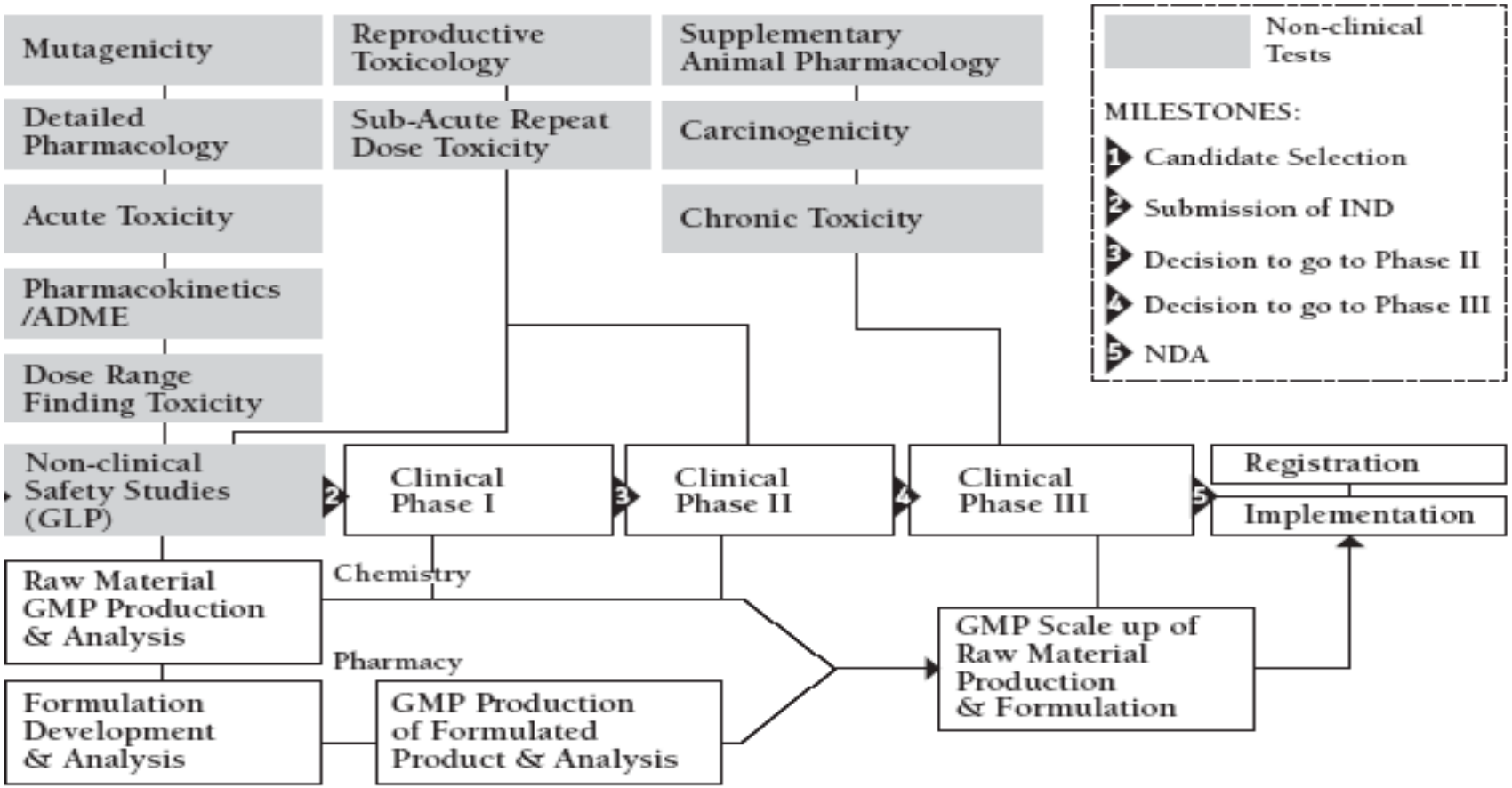
- *Studio delle proprietà farmacocinetiche*
  (assorbimento, distribuzione, eliminazione, analisi dei metaboliti)

- *Studio delle proprietà farmacodinamiche*
  (effetti, meccanismo d'azione, relazione dose-effetto e tempo-effetto, calcolo del margine terapeutico)

STUDI DI SICUREZZA

- *Studio tossicologico*
  (tossicità acuta, cronica, azione sulla fertilità, studi di teratogenesi, mutagenesi, cancerogenesi)

COMPONENTS OF PRODUCT DEVELOPMENT



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Notice To Applicant

NTA, Volume 2B

COMMON TECHNICAL DOCUMENT, CTD

This guidance recommends a specific organization for the placement of study reports and related information to simplify preparation and review of dossiers and to ensure completeness.

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CTD Overall Organisation

- *Module 1* → *Region specific, not part of the CTD*

- *Module 2 - Summaries*
- *Module 3 - Quality*
- *Module 4 - Non-Clinical*
- *Module 5 - Clinical*

→ *common to all regions*

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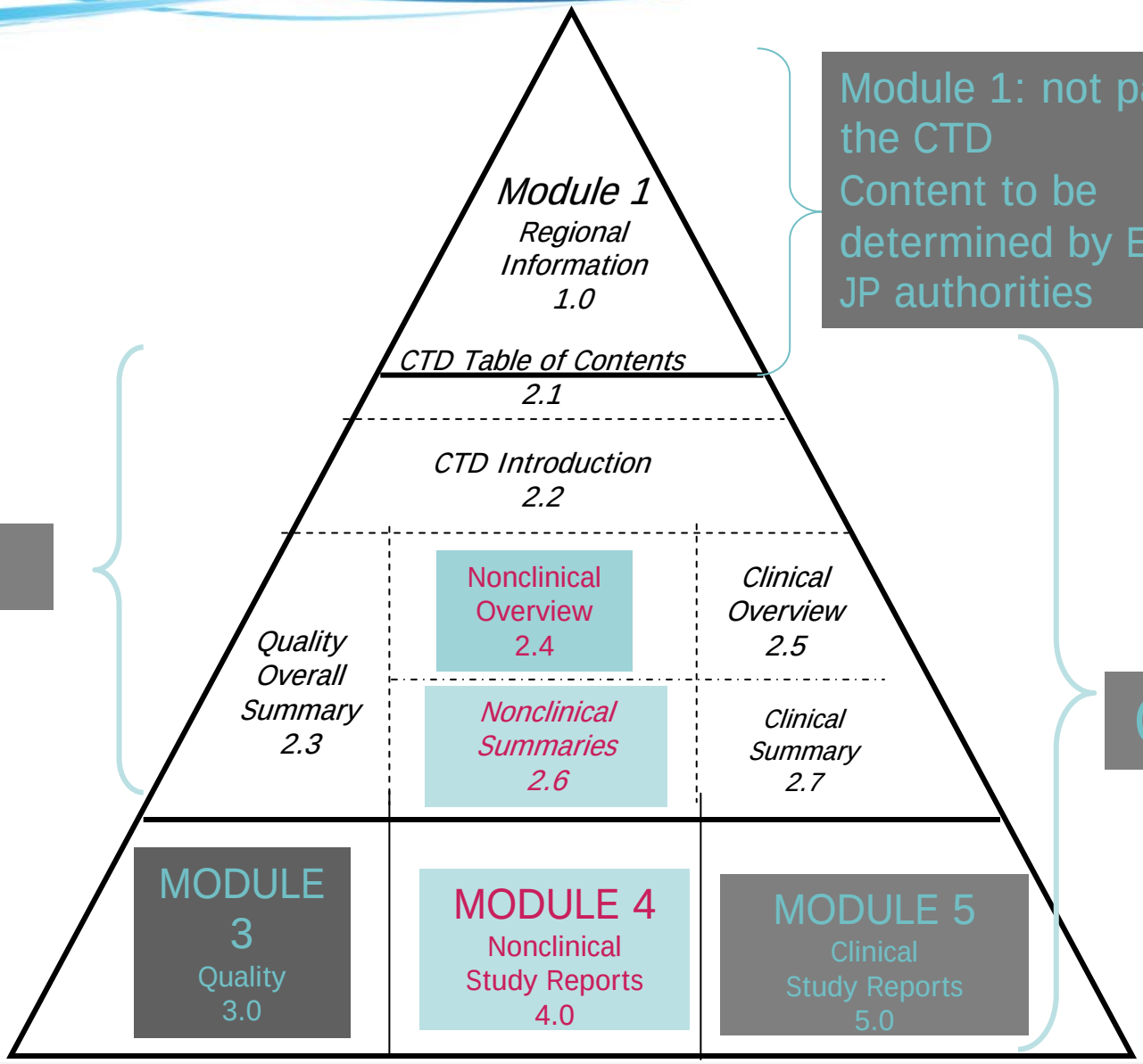

Module 1: not part of the CTD
Content to be determined by EU, US, JP authorities

Module 2:

CTD

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Module 4
Non clinical study reports

- Pharmacology
- Pharmacokinetics
- Toxicology

Module 4
4.2.3 Toxicology

- Single-Dose Toxicity
- Repeat-Dose Toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and Developmental Toxicity
- Local Tolerance
- Other Toxicity Studies (Antigenicity, Immunotoxicity, Mechanistic studies, Dependence, Metabolites, Impurities, Others)

Module 4
4.2.3 Toxicology

Toxicokinetics

-Assessment of systemic exposure (blood levels) in animal toxicity studies

-To assess clinical relevance of toxicity findings

-Usually an integral part of the toxicity studies

Module 4
4.2.3 Toxicology

Single-Dose Toxicity

- in two mammalian species
- using clinical and parenteral route

Repeat-Dose Toxicity

- in two mammalian species including one non-rodent;
- the duration of the studies should be equal or exceed the duration of the clinical trials;
- order by species, by route, by duration;
- including supportive toxicokinetics evaluations

Doses up to a maximum of 1000mg/kg/day (mean exposure margin of 10-fold to the clinical exposure should be considered)

Module 4
4.2.3 Toxicology

Genotoxicity

- complete bactery of in vitro and in vivo studies before the phase II
- in vitro studies prior the first human dose (Ames Test)
- in vivo studies including supportive toxicokinetics evaluations

Module 4
4.2.3 Toxicology

Carcinogenicity

- Needed if cumulative lifetime exposure is > 6 months
- Including supportive toxicokinetics evaluations
- Studies in 2 species (rats 24 months and mice 18 months)
- CAMM (p53; RasH2; hgtf)

Module 4
4.2.3 Toxicology

Reproductive and Developmental Toxicity

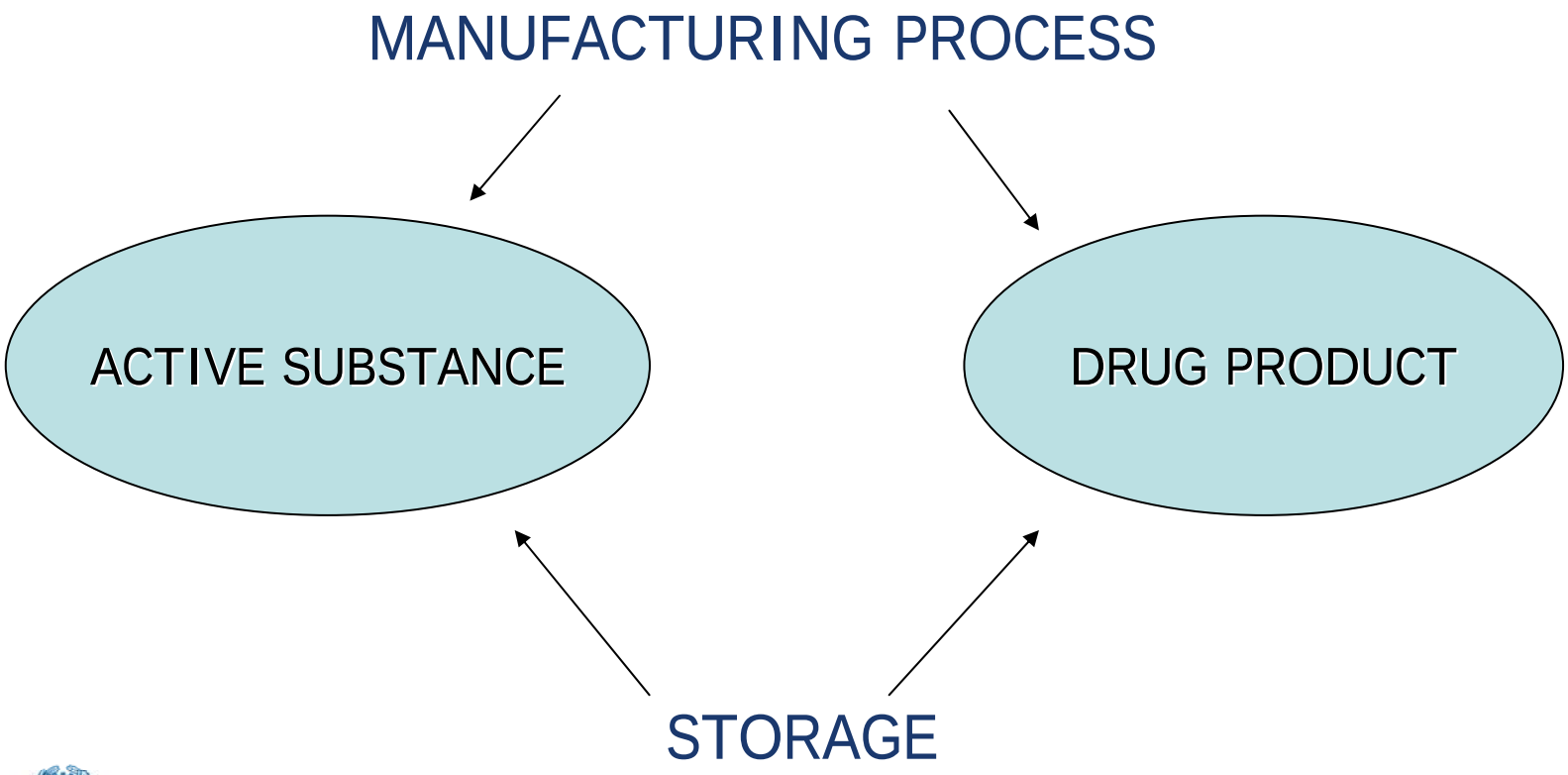
- Range-finding studies and supportive toxicokinetics evaluations
- Fertility and early embryonic development (one species, male and female rats)
- Embryo-fetal development (2 mammalian species, generally rat and rabbit)
- Prenatal and postnatal development, including maternal function
- Studies in which the offspring (juvenile animals) are dosed and further evaluated

Module 4
4.2.3 Toxicology

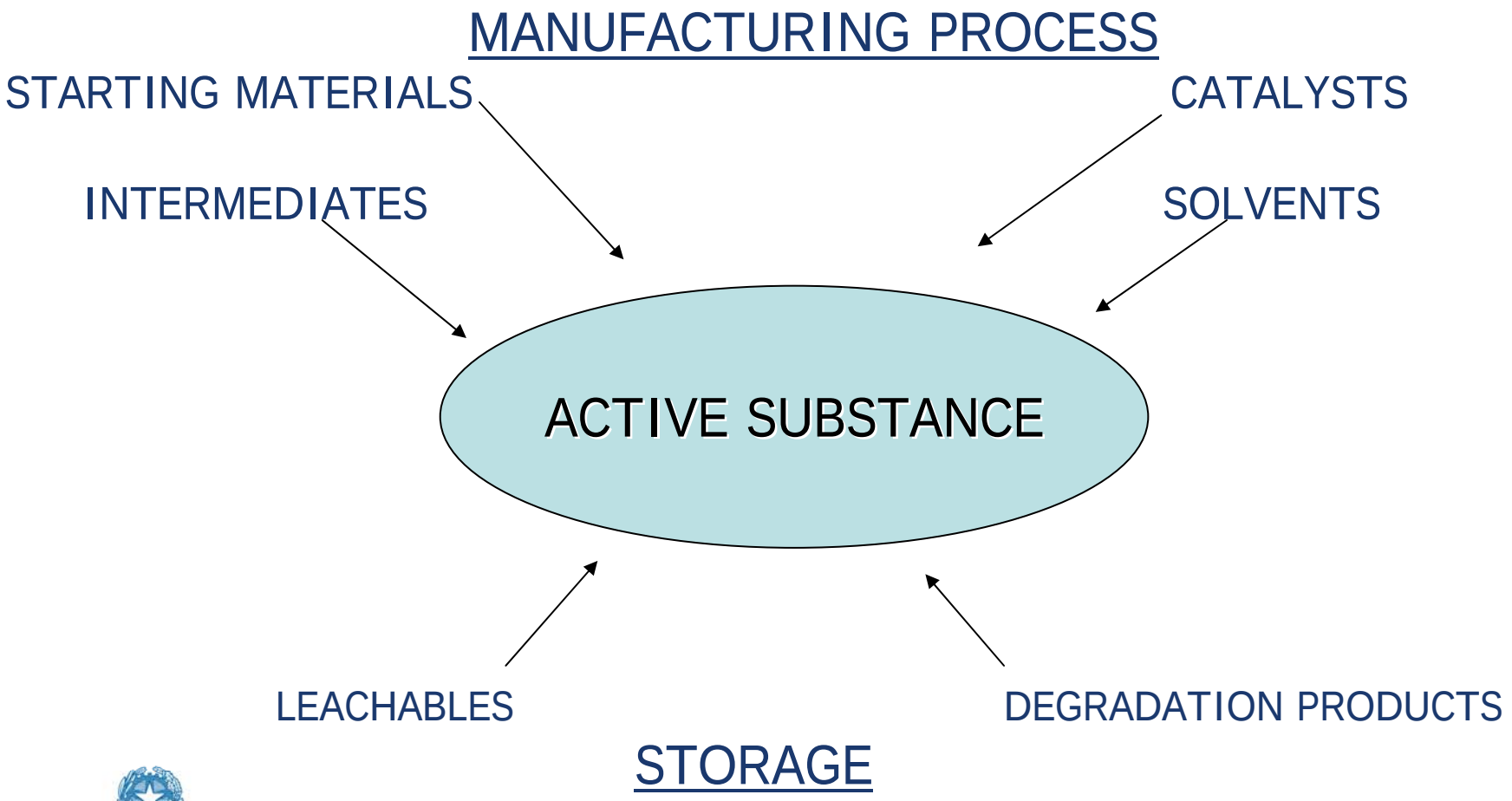
Other Toxicity Studies:

- Antigenicity
- Immunogenicity
- Mechanistic studies
- Dependence
- Metabolites
- Impurities

SOURCES OF DRUG IMPURITIES

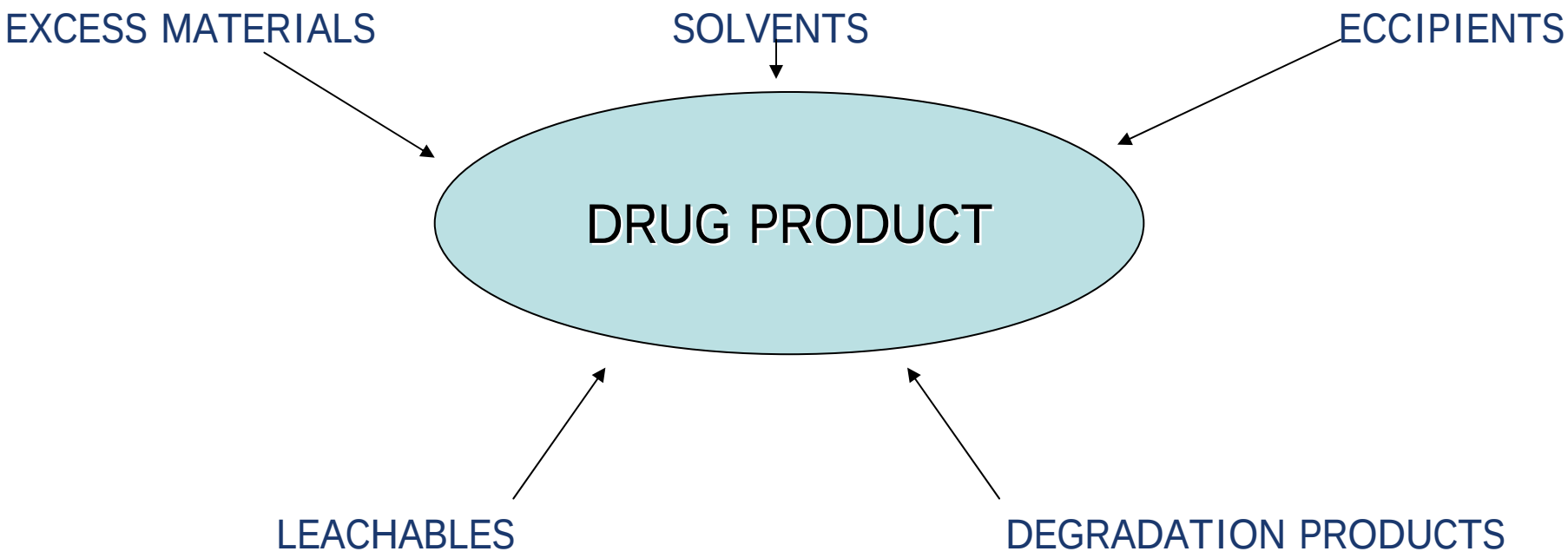


SOURCES OF DRUG IMPURITIES



SOURCES OF DRUG IMPURITIES

MANUFACTURING PROCESS



STORAGE

GUIDELINES ON IMPURITIES

ICH

- Impurities Testing: Impurities in New Drug Substances (ICH Q3A)
- Impurities in New Medicinal Products (ICH Q3B)
- Impurities: Residual Solvents (ICH Q3C)

CHMP

- Specification Limits for Residues of Metal Catalysts CPMP/SWP/QWP/4446/00
- Control of Impurities of Pharmacopoeial Substances CPMP/QWP/1529/04
- Annexes to Specifications for class 1 and class 2 residual solvents in active substances CPMP/QWP/450/03
- Limits of genotoxic impurities CPMP/SWP/5199/02 EMEA/CHMP/QWP/251344/2006

ALARP PRINCIPLE

THE FORMATION OF DRUG IMPURITIES SHOULD BE AVOIDED OR OTHERWISE LIMITED TO THE MINIMAL AMOUNT DURING THE MANUFACTURING PROCESS

(to a levels “as low as reasonably practicable”, where avoiding is not possible)

“The quality of drug substances and drug products is determined by their design, development, in process control, GMP controls, and process validation, and by specification applied to them throughout development and manufacture.”

ICH TopicQ6A Guideline“Test procedures and acceptance criteria for New Drug Substances and New Drug Products: Chemical Products”.

TOXICOLOGICAL QUALIFICATION OF IMPURITIES

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. The applicant should provide a rationale for establishing impurity acceptance criteria that includes safety considerations.

QUALIFIED IMPURITIES

- The level of any impurity present in a new drug substance that has been adequately tested in safety and/or clinical studies would be considered qualified.
- A level of a qualified impurity higher than that present in a new drug substance can also be justified based on an analysis of the actual amount of impurity administered in previous relevant safety studies.
- Impurities that are also significant metabolites present in animal and/or human studies are generally considered qualified.

ICH GUIDELINES ON IMPURITIES

- ICH Q3A and Q3B**:** regulate the levels of impurities by setting generic threshold levels for reporting, identification, and qualification.

- ICH Q3C: introduces some toxicological principles by assigning the residual solvents to different classes-each representing different levels of toxicological concern-and by presenting the permissible daily exposure (PDE) method.

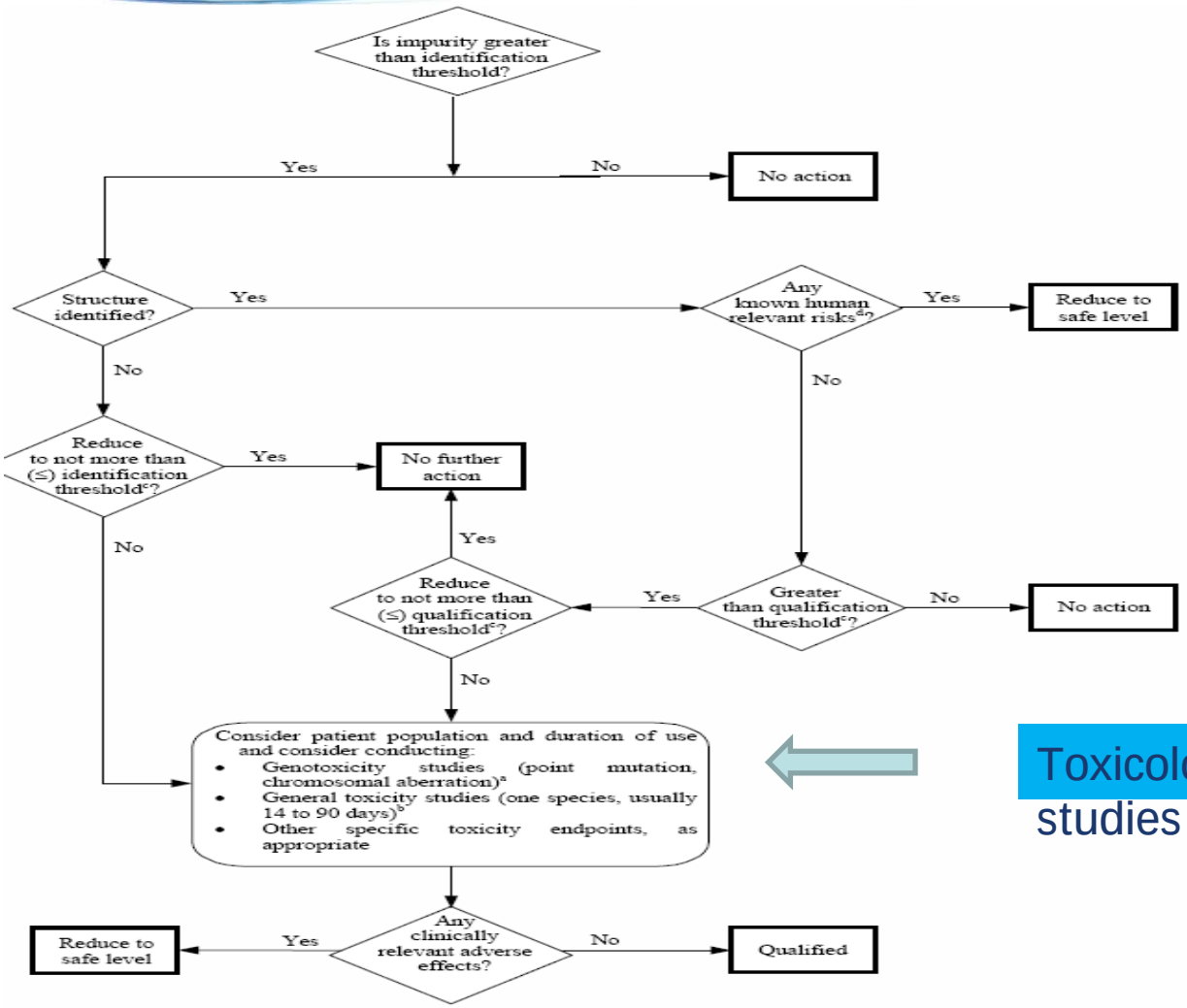
ICH Q3A: Impurities in New Drug Substances

- Exception for genotoxic impurities

Maximum daily dose	Identification Threshold	Qualification Threshold
≤2 g/day	0.10% or 1 mg TDI (Whichever is lower)	0.15 % or 1 mg TDI (Whichever is lower)
>2g/day	0.05%	0.05%

ICH Q3A Decision Tree

For qualification of impurities when thresholds are exceeded



Toxicological studies

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ICH Q3B: Impurities in New Drug Products

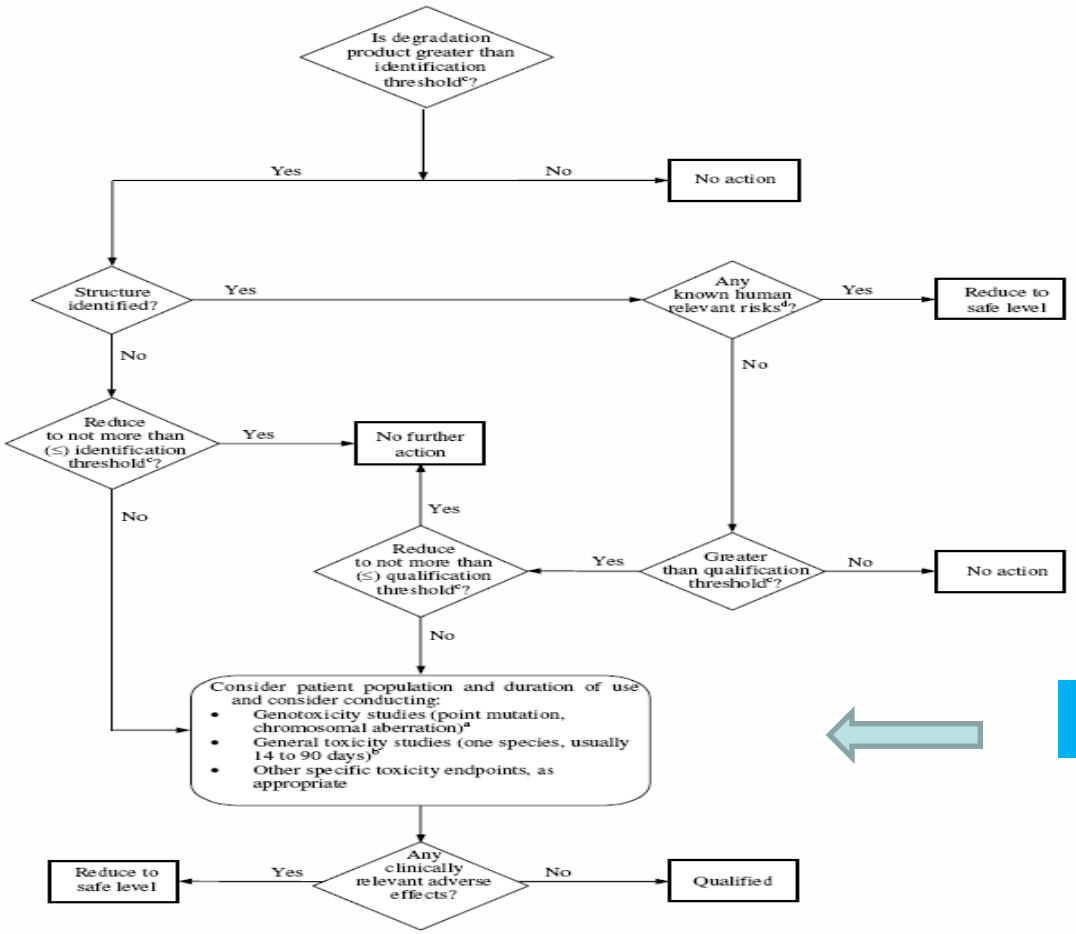
- Degradation products of the active ingredient on storage
- Reaction products of the active ingredient with an excipient, container or closure system

Maximum daily dose	Qualification Threshold
< 10 mg	1% or 50µg TDI (whichever is lower)
10 mg -100 mg	0.5% or 200 µg TDI (whichever is lower)
>100 mg -2 g	0.2% or 3 mg TDI (whichever is lower)
> 2g	0.15%

ICH Q3B Decision Tree

For qualification of impurities when thresholds are exceeded

Attachment 3: Decision Tree for Identification and Qualification of a Degradation Product



Toxicological studies

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RESULTS

If genotoxicity assays with the drug substance were negative, the impurities contained in the drug substance were generally considered qualified up to the concentration present in the batch used in the assays.

ICH Q3C: Residual Solvents

- Remove or limit content sufficiently in order to meet
  - product specification
  - good manufacturing practices
  - safety requirements

ICH Q3C: Residual Solvents

Three categories based on their safety (i.e. 'Permissible Daily Exposures'):

- Class 1: unacceptable toxicity (includes known carcinogens) should be avoided unless product gives significant therapeutic benefit (anti-cancer) e.g. benzene (2ppm), carbon tetrachloride (4ppm)

- Class 2: irreversible toxicity including neurotoxicity, teratogenicity and non-genotoxic carcinogens, exposure limited to <50 mg/day (5000ppm), eg, cyclohexane, pyridine, methanol

- Class 3: low toxicity, exposure should be limited to 50 mg/day, but higher exposure may be justifiable on case by case basis eg acetic acid, ethanol, DMSO

Metals / Catalysts

CPMP/SWP/QWP/4446 -00

- Acceptable limits for residual metals arising from use of catalysts in synthesis of pharmaceuticals (e.g. Ni, Cu, Cr)
- Being developed using same rationale as for Q3C (i.e. PDE's-but taking dietary exposure into account)
- If not listed, use 10 ppm default, unless data suggests otherwise

CONTAINER CLOSURE SYSTEM

Impurities arising from excipients present in a new drug product or extracted or leached from the container closure system are not covered by this guidance

Extractable

– Any chemical species that can be removed from a packaging component under laboratory conditions (e.g., component is cut in pieces and incubated with solvent).

Leachable

– An extractable that actually migrates into a drug product under storage conditions.

A rationale, based on available toxicological information, should be provided to support acceptance criteria for components in terms of the extractable profiles

Genotoxic impurities

"Genotoxic" in general means that there are positive findings in established in vitro or in vivo genotoxicity tests with the main focus on DNA reactive substances that have a potential for direct DNA damage.

Genotoxic impurities

The identification and qualification thresholds given in the ICH Q3A and Q3B only apply to "standard" impurities that do not exhibit unusually high toxicity.

For highly toxic impurities, identification is required even at levels below the defined identification threshold.

How to do it?

- Screening should occur during the phase of preclinical development
- All available knowledge of the synthesis and chemistry of the API should be used to identify the potential formation of toxic impurities for alerting structure

Genotoxic impurities

Genotoxic compounds with a threshold mechanism

PDEs can be calculated

(based on the identification of NOEL (or LOEL) and use of uncertainty factors)

Genotoxic impurities

Genotoxic compounds with no threshold mechanism identified

ALARP principle

TTC approach

A pragmatic approach to recognise that the presence of very low levels of genotoxic impurities is not associated with an unacceptable risk

Threshold of Toxicological Concern (TTC)

THE TTC IS A COMMON EXPOSURE LEVEL FOR ANY UNSTUDIED CHEMICAL THAT WILL NOT POSE A RISK OF SIGNIFICANT CARCINOGENICITY OR OTHER TOXIC EFFECTS

- TTC estimated to be 1.5 µg/person/day (corresponds to a 10^{-5} lifetime risk)
- TTC for high potency carcinogens 0.15 µg/person/day (corresponds to a 10^{-6} lifetime risk)
- TTC value can be higher under certain conditions
  - short-term exposure
  - life-threatening conditions with no safer alternatives
  - when life expectancy is less than 5 years
  - if the impurity is a known substance and human exposure will be much greater from other sources (eg, food).

$$\text{Concentration limit (ppm)} = \frac{\text{TTC [µg/day]}}{\text{dose (g/day]}}$$

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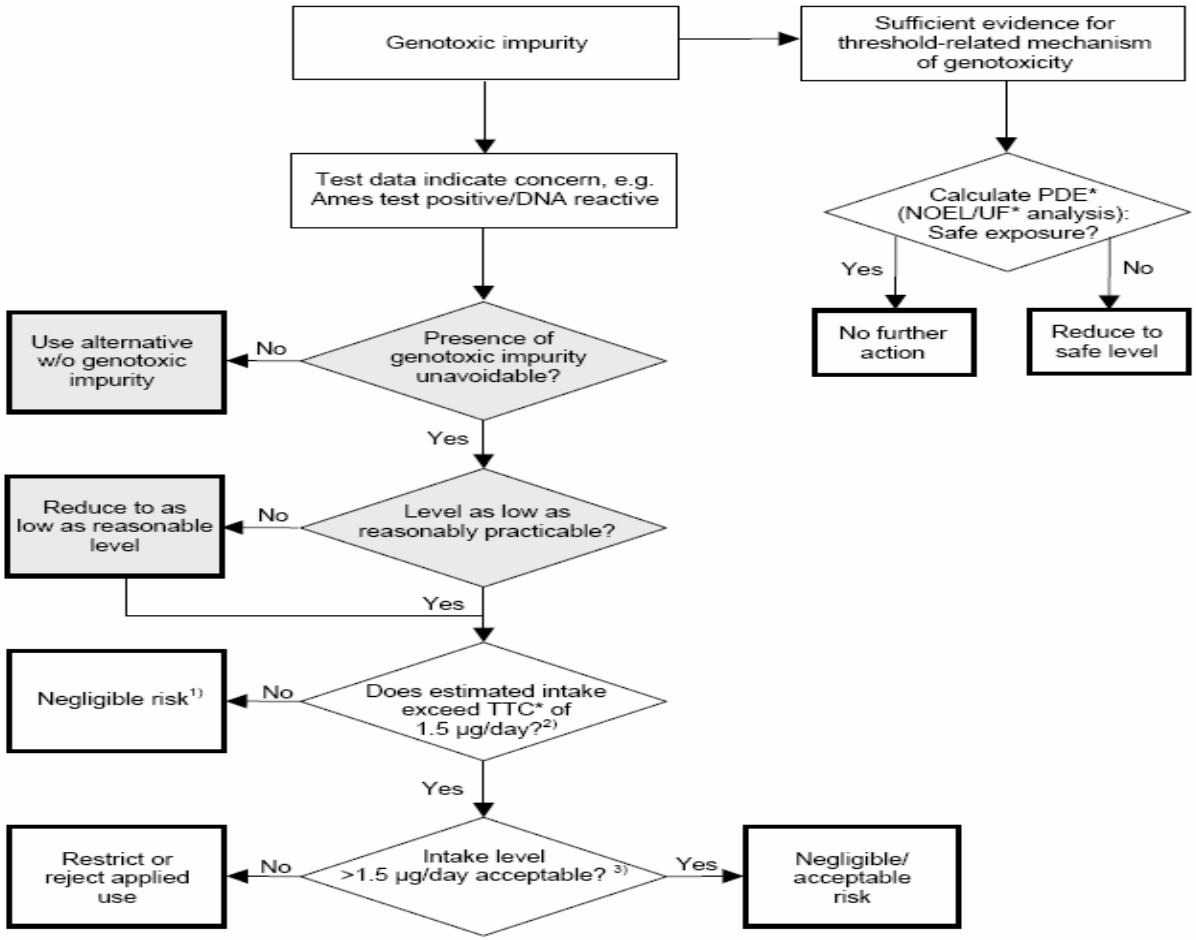
Threshold of Toxicological Concern (TTC)

TTC should not be used

- For high potency genotoxic carcinogens:
  - aflatoxin-like-
  - N-nitroso-
  - azoxy-compounds

- For carcinogenic impurities where adequate data exist and allow for a compound specific risk assessment

Genotoxic impurities Decision Tree



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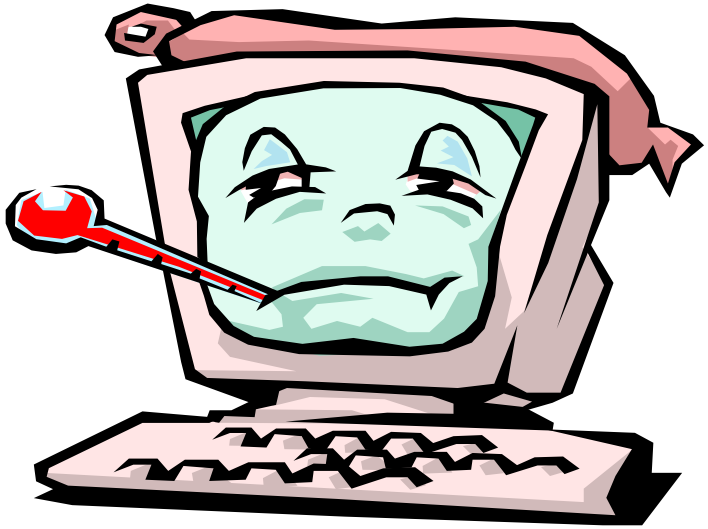
the absence of genotoxicity does not necessarily means absence of cancerogenicity

MEDICINES ARE SAFE?



Grazie per l'attenzione

CONTATTI

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