

**When to
Stop**

Dose

Escalation:

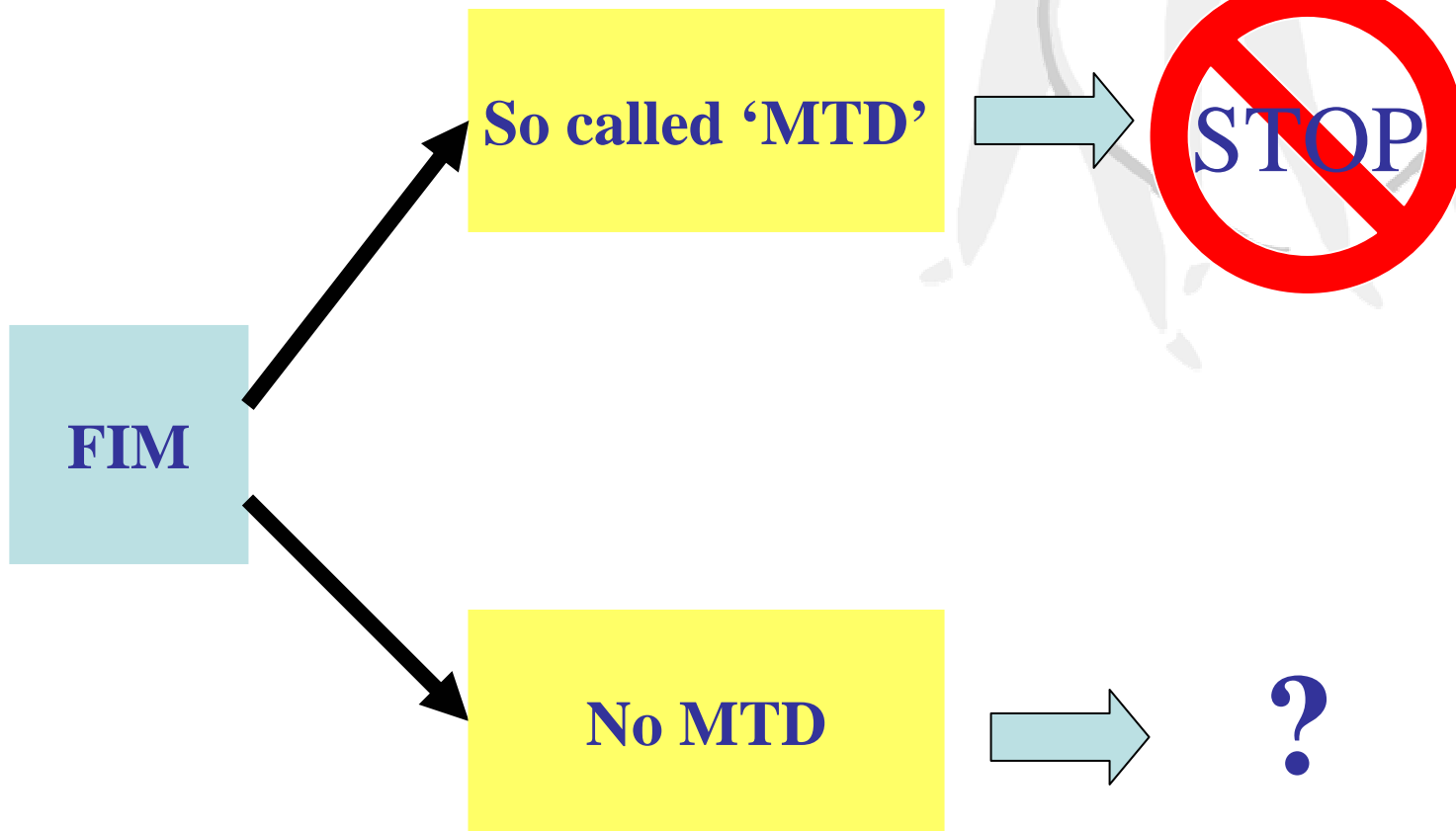
MTD, MLD or ?

Henri CAPLAIN

First Joint Annual Meeting, AGAH – Club Phase 1

STRASBOURG, France





WHY WE NEED TO REACH THE MAXIMUM TOLERATED DOSE IN ASCENDING DOSE STUDY IN EARLY PHASE I ?



Clinical and Exploratory Pharmacology – HC
AGAH/CP1 – 17/Mar/05



THE MAXIMUM TOLERATED DOSE IS ONE OF THE OBJECTIVES OF EARLY PHASE I



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Why MTD in early Phase I?

Important concept in New Chemical Entity (NCE) development

Helps:

- to determine the optimal dose range for efficacy clinical trials (Phase II/III)
- to ensure both that the doses tested in Phase II are **SAFE** and that the largest potentially efficacious dose range is evaluated

Lack of care in determining the MTD can lead to design flaws and inconclusive results in patients



Other reasons

COVER THE EXPOSITION THAT WE COULD REACH AT THERAPEUTIC DOSAGE IN PARTICULAR SITUATIONS:

- **Drug-drug interaction**
- **Food interaction**
- **Special population: obese, renal insufficiency, hepatic failure**
- **....**

COVER THE EXPOSITION IN REPEATED DOSE

- **Particularly in case of accumulation**
- **For the Thorough ECG studies at therapeutic and supra-therapeutic expositions**

NORMALLY IT IS THE ONLY CONDITION OF ACUTE OVER-DOSAGE DURING THE DRUG DEVELOPMENT: INTEREST FOR DEVELOPMENT IN DEPRESSION



Risk to do not have a right MTD

If the MTD is set too high, patients could be exposed to unsafe doses, and the resulting intolerance adverse events may even lead to discontinuation of the compound's development

If the MTD is set too low, placebo or sub-therapeutic doses could be administered to hundreds of patients in Phase II efficacy studies, wasting years of development on no-effect studies



**HOWEVER THE MTD
SHOULD NOT BE
SYSTEMATICALLY
SEARCHED IN HEALTHY
SUBJECTS**



WHY ?

Is it really ethical to search the MTD in healthy subjects?

Mainly for safety reasons

- No reversibility of potential adverse events
- No potential monitoring of adverse events (seizure)
- Seriousness of the potential adverse events
- Steep dose-response curve in animals
- But also for PK reasons:
 - ┌ Upper-linearity
 - ┌ Saturation of exposure
 - ┌ Exposition higher than NOAEL, Toxic exposition or Lethal exposition in animals (**warning on the predictive value**)



WHY ?

Alternative tools:

- **Accurate** biomarkers of activity in humans (anti-coagulants)
- Exposition reached in toxicokinetics (but not totally predictive of the human MTD)
- Exposition reached on **pertinent** pre-clinical models of activity
- PK/PD relationship (warning: cannot allow to determine the future therapeutic benefit of the NCE)

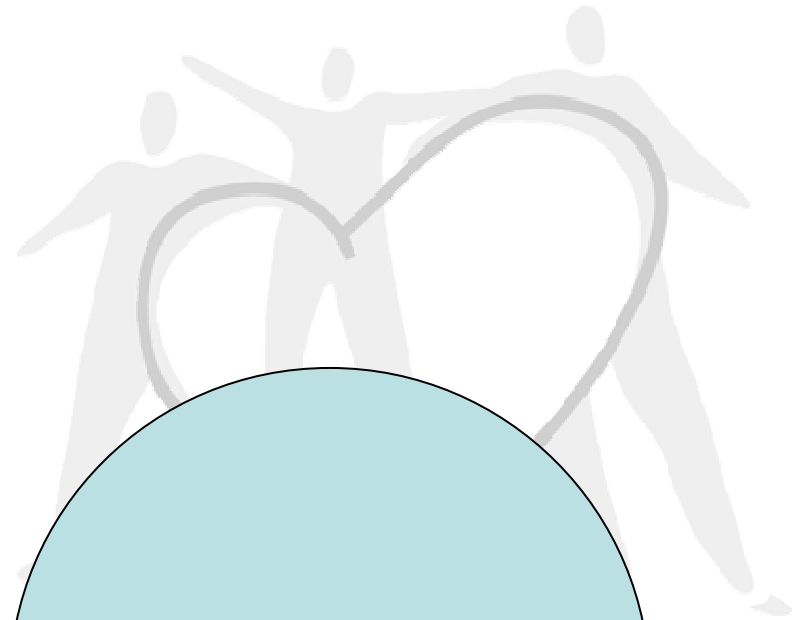
e.g.: IMAOB with platelet MAOB activity and PETscan



BENEFIT = 0

=

RISK = 0



A key question at the end of the study is “Have you reached dose levels of the compound in plasma that you would expect to be efficacious in patients and is the safety profile acceptable at this dose ?”



LIMITS OF THE MAXIMUM TOLERATED DOSE IN HEALTHY SUBJECTS



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MTD definition

MAXIMUM TOLERATED DOSE:

- **Medicine: the highest dose level eliciting signs of toxicity without having major effects on survival relative to the test in which it is used (source: European Union, Webster's Dictionary)**
- **German: Maximal Verträgliche Dosis, Einzelmaximaldosis**
- **French: Dose Maximale Tolérable ou tolérée**



MTD DEFINITION

The MTD has been variously defined as:

- The maximum dose administered during study that elicits no toxicity (Carter SK, Cancer 1997)
- The dose that produces mild to moderate sublethal toxic effects in a significant percent of individuals (Geller NL, Cancer Invest 1984)
- Some percentile of the tolerance distribution (Storer BE, Biometrics 1989)

What is a significant percent of individuals?

Cancer or biostat definitions, clearly not adapted for HS



Other proposed definition

The MTD for a serious disease was also defined by reaching the MID (Cutler NR, 2000)

- The dose at which limiting adverse events (defined by objective criteria) occur in most subjects ($\geq 50\%$)
- Or the dose at which a serious adverse event (defined as medically unacceptable in the population) occurs in one or more subjects (seizure or severe hypotension with associated cardiac changes)



Definition of tolerable or intolerable ?

Obviously for some drugs the side effects that will be tolerated will not be as extreme as the side effects that would be tolerated for other drugs (cancer, HIV,...)

Oftentimes Phase I trials in other drugs than cancer drugs fail to formally define the concept of MTD beyond the **vague concept of tolerable or intolerable** at a certain dose level

Unacceptable adverse events constitute an unacceptable medical risk compared with the indication

A **dose-limiting adverse** event is one that interferes with function but is not considered serious compared with the indication



WHAT IS THE PREDICTIVITY OF MTD IN HEALTHY SUBJECTS FOR PATIENTS STUDIES



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Sometimes poor prediction

The question surrounding the issue of normal subjects versus patients should address whether or not MTD estimate from normal volunteers predicts the MTD in patients (antipsychotic agents)

Could signs of efficacy in patients manifest as tolerance issues in normal subjects (antihypertensive)

Also true for:

- Alzheimer Disease (AD)
- Major Depression Disease (MDD)
- Generalized Anxiety Disease (GAD)
- Cardio-Vascular disease
- Hormonal disease



Tools in case of poor prediction

Start Phase I directly in patients (as in HIV or oncology for other reasons)

Introduced patients very early in Phase I to determine the MTD in the target population

- Bridging studies for CNS compound (Cutler NR)
- Hypertensive patients
- Asthmatics patients
- Dyslipidemic patients
- Diabetics
- Etc ...



WHAT IS THE REALITY ?



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CRO 1

	2000	2001	2002	2003	2004
End of study	0	0	0	0	7
Stop on NOAEL	0	1	0	0	2
Stop for MTD	2 (GI, CNS)	1 (CV)	3 (CVx2, immun.)	1	1 (CV)
Other	1	1	1	2	0



CRO 2

	40 TDU
MTD	24
Other reasons	16
Amendment for complementary dose	10



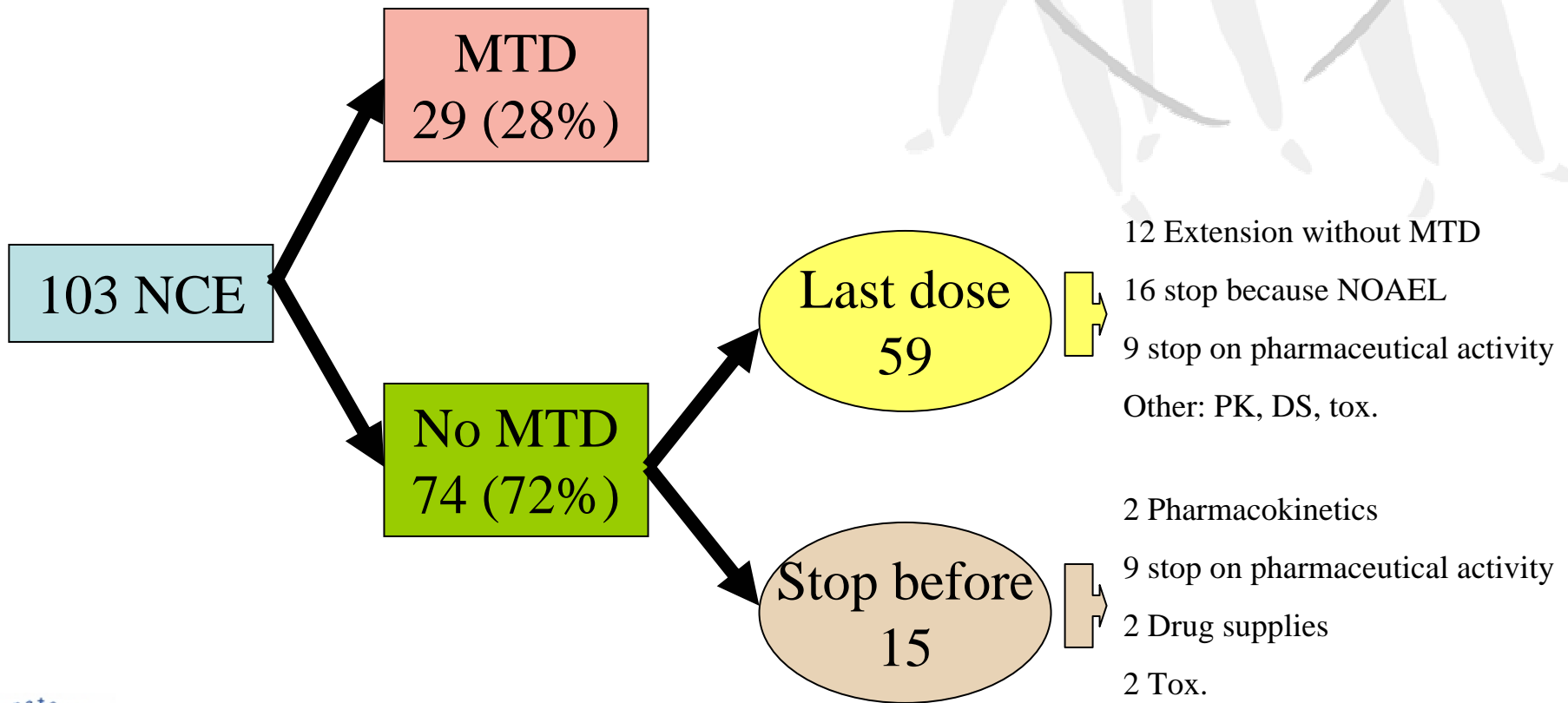
CNS, GI, CV, BW



Tox data, saturation PK



Personal Experience as Investigator (1992 to 2002)



Club Phase Survey

April 1995

Academic, Industrial, Investigators

11 answers to the questionnaire: 6 definitions of the MTD:

- Number of subject with an adverse event (minors, moderate of the same type, serious)
- Vague: tolerability notions, probability more acceptability than tolerability
- Definition of intolerance
- Subjectivity of the toxicity of the NCE:
 - ┌ Theoretic toxicity potential of the NCE (in vitro and animals data, chemical class and pharmaceutical activity)
 - ┌ Level of comfort for the Investigator and the sponsor
 - ┌ Cultural and geographical differences (NA, Western Europe, Japan)



Club Phase 1 Survey



MTD on the last 5 FIM: 7 answers

- 2 to 4 by answer
- 24/35 = 68%

All the dose planned in the protocol used: 7 answers

- 3 to 5 by answer
- 23/35 = 65%



Literature

Chaikin P (J Clin Pharmacol 2000)

- **36% of MTD reached (all therapeutic axis without oncology)**
- **In the majority of the other cases, the MTD was not reached due to the benign toxic profile of the NCE**
- **Stop for other considerations than MTD:**
 - 【 Pharmacokinetic: non-linearity, high exposition, saturation
 - 【 Pharmacological activity (e.g. anticoagulant)
 - 【 Galenic reasons: number of capsules, number of puff for intranasal spray, ..
 - 【 Other reasons



**CONCLUSION:
PRIORITY TO THE
SAFETY IN HEALTHY
SUBJECTS WHERE THE
BENEFIT/RISK RATIO IS
PARTICULAR**



YES TO SEARCH THE MTD OR PREFERALLY THE MAD



Safety margin

More comfortable for the following parts of the development (DDI, Special populations, ...)

Some indications where it is interested to have acute over-dosage (MDD)

In well survey and controlled specialized unit (“SKILLED HANDS”)



HOWEVER “NOT AT ALL COSTS”

In HS: the benefice/ratio must be balanced and there is tolerability studies and not toxicology studies (remember: benefit = 0, risk = very low +++)

The security of subject **MUST** stay a priority

Depending of the toxicology of the drug:

- reversible or irreversible activity
- reversible or irreversible Aes (sequelae)
- Monitoring of potential Aes
- Existence of an antidote
- Potential severity

Must to be challenged with the indication and target population

