

Is priority to **MTD**

- maximal tolerated dose -

the **best** way ?

(Early) development is facing two major questions:

**Safety**

**Activity**

Early development is facing two major questions:



Safety  $\rightarrow$  MTD

Activity  $\rightarrow$  mad

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M  
A  
R  
G  
I  
N

# *Safety is a societal priority*

Safety concerns: major parts of all recent recommendations and guidelines

*FDA MRSD guidance, AFSSAPS, BfArM, MHRA, EMEA draft guideline*

More and more → minimizing risk !

...thus knowing the potential safety...

...therefore **determining the MTD !**

# MTD ... a suitable concept

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Defining the maximum tolerated dose

J Clin Pharmacol 1997;37:767

**Def:** « The highest safe dose  
and maximal usable dose »

## **MTD a ... suitable concept**

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## **MTD a ... realistic strategy**

Sanofi-Aventis survey

101 compounds moved to man - FIMs

Phase I MTD rate: 58 %

**MTD a suitable concept**

**MTD a ... realistic strategy**

**Moreover ... a secured strategy**

**101 compounds**

**12 SAEs, no death, all fully reversible**

***MTD: a simple & adaptative strategy ...  
...in practicing early development***

To progress step by step from:

Young male HV Single Dose ...	'MTD 1'
to Multiple Dose ...	'MTD 2'
to targeted population - asthma ...	'MTD 3'
or to elderly, then Alzheimer...	'MTD 3&4'
and ...	
finally to phase ...2...3	MTDs

# *MTD: A limited strategy ?*

\*\*\* Yes, really if:

Hysteresis, Bell or U shape activity profile

\*\*\* Yes, partly:

Survey: 42% without MTD

But ! always, at least: a MAD

- maximal administered dose -

well really, already a

...maximal usable dose...

...and a safe one !

Early development is facing two major questions:



Safety  $\rightarrow$  MTD

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## *Activity: The finest scenario*

Biomarker (pharmacological marker)

→ POP-POM-Phco activity-PD-POC

→ establishing effect/activity

→ selecting doses

particularly the anticipated

minimal active dose

before embarking to 2B dose ranging st.

## *Activity: a 'painful' reality*

### Biomarker(s)

- Often do not exist ...first in class !
- Support poor/no relevance to activity
- May get validation ...  
...only from Ph 3 pivotal study result

## *Pharmacology...an other weakness*

Pharmacology in FIMs may predict

- targeted activity

but

- not tolerability: 9% in the survey

*The optimal sequence is well...*

*... MTD preceding Activity*

Knowing « well tolerated » doses is preferable

→ before running: \* pharmacology studies

\* *phase 2 studies*

- no stress to subjects
- no intercurrent bias related to safety
- *prevent patients poor tolerability & minimize risk*
- *avoid dropouts*
- *use maximal dose to activity assessment*

# Thus...

- MTD and pharmacology are  
PARTNERS and not ENEMIES
- But, in processing, MTD is to keep in  
priority – starting first before pharmacolgy
- MTD  
is holding out one's hand  
to pharmacology...

*MTD*

*being holding out ones's hand  
to pharmacology...*

