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 → **MTD**

Activity → **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

® CUTLER et al

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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® CUTLER et al Defining the maximum tolerated dose J Clin Pharmacol 1997;37:767

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 → **MTD**

Activity → **mad**

M A R G I N

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 preceeding Activity

Knowing « well tolerated » doses is preferrable

→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…