

Key Aspects of Non-Clinical Pharmacology and Pharmacokinetics in the Evaluation of Safety

David R Jones

(david.jones@mhra.gsi.gov.uk)

Expert Pharmacotoxicologist,

Medicines and Healthcare products Regulatory Agency (MHRA), UK

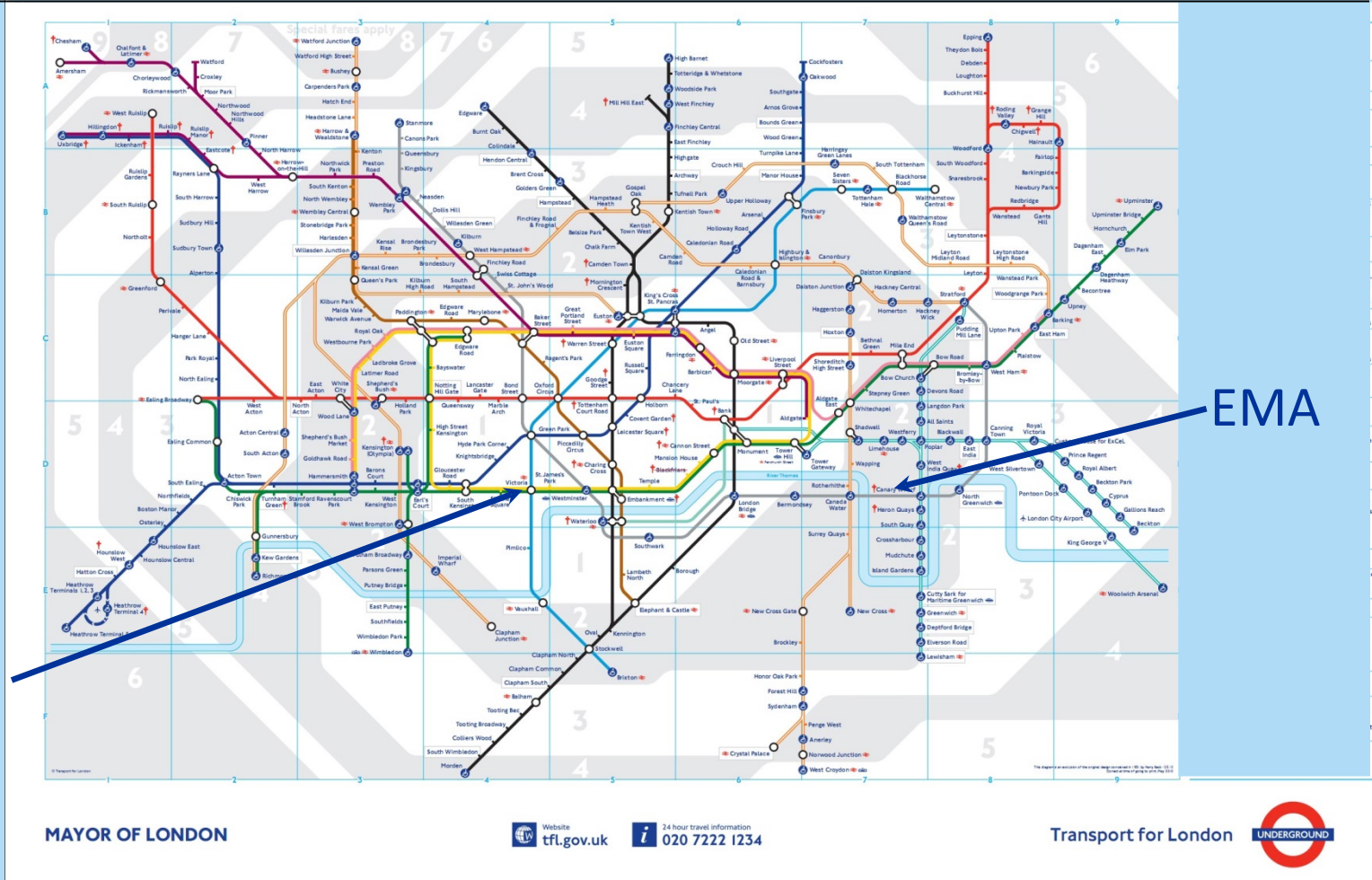
**ANY OPINIONS EXPRESSED IN THIS
PRESENTATION ARE MY OWN,
AND MAY NOT NECESSARILY BE SHARED BY
OTHER ASSESSORS AT THE MHRA OR SWP.**

CROWN COPYRIGHT 2016

The materials featured within this MHRA presentation are subject to Crown copyright protection for this event. Any other copy or use of Crown copyright materials features in this presentation, in any form or medium, is subject to prior approval of the MHRA which has Delegated Authority from Her Majesty's Stationery Office (HMSO) to administer Crown copyright for MHRA originated material. Applications should be in writing, clearly stating the proposed use / reuse of the information, and should be sent to the MHRA at the following address: Conference and Education Function, MHRA, 151 Buckingham Palace Road, London SW1W 9SZ or e-mail speakers@mhra.gsi.gov.uk. You may not sell or resell any information reproduced to any third party without prior agreement. The permission to reproduce Crown copyright material does not extend to any material in this pack which is subject to a separate licence or is the copyright of a third party. Authorisation to reproduce such material must be obtained from the copyholders concerned.

Regulatory Guidelines





EMA

MHRA



MHRA

Regulatory guidelines are like the modern map of the London Underground.

They don't completely represent the "real" world.

There's almost always more than one way to reach an objective and the recommended route might not be the one you should follow!



Samuel Johnson said “Patriotism is the last refuge of the scoundrel.”



I say “Rigorously following Regulatory Guidelines is the last refuge of those who don’t know how to develop medicines!!.”

DO NOT STRICTLY FOLLOW A REGULATORY GUIDELINE WHEN THERE IS A GOOD SCIENTIFIC RATIONALE NOT TO!

General points:

- Guidelines are generally written in order to provide an element of flexibility and not to place undue legislative restraints on scientific progress.
- All studies should be conducted according to acceptable current protocols. Each study should be planned and designed taking into account the properties and indications of the drug concerned.



Pharmacology

The incident during a FIH clinical trial with multiple study parts in Rennes, France, in January 2016 warranted the existing EU guidance to be extended to address the more complex clinical trials seen today and the non-clinical and emerging clinical PK, PD and safety data requirements to support them.

The draft of the revised guideline is scheduled to be released for a 3-month public consultation by the end of 2016.

A workshop with stakeholders is planned for early 2017.

The final guideline is expected to be adopted by CHMP in 2017.



**ICH Topic M 3 (R2)
Non-Clinical Safety Studies for the Conduct of
Human Clinical Trials and Marketing Authorization for Pharmaceuticals**

**SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS
S7A**

**ICH guideline S6 (R1) – preclinical safety evaluation of
biotechnology-derived pharmaceuticals**

**ICH Topic S9
Nonclinical Evaluation for Anticancer Pharmaceuticals**

Pharmacology can be divided into three categories: primary pharmacodynamics, secondary pharmacodynamics and safety pharmacology.

Primary pharmacodynamics can be defined as studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target.

Secondary pharmacodynamic studies (previously referred to as general pharmacology) can be defined as studies on the mode of action and/or effects of a substance not related to its desired therapeutic target.



Safety pharmacology studies are defined as those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above.



Studies should be conducted in a relevant animal model.

The demonstration of relevance of the animal model(s) may include comparison with humans of:

Target expression, distribution and primary structure.

However, a high degree of homology does not necessarily imply comparable effects!

PD studies should address the mode of action, and provide knowledge on the interaction of the IMP with the intended target as well as other related targets.

These data will help to characterise the pharmacological effects and to identify the most relevant animal models.

The selectivity and specificity of the IMP should be critically evaluated and documented.



Pharmacodynamics

Binding profile and occupancy to receptors or enzymes, functional consequences (agonistic/antagonistic; stimulatory/inhibitory), including appropriate cell signalling;

(Ir)reversibility of effects, duration of effect, physiological turn-over of the target;

Data on the functionality of additional functional domains in animals, *e.g.* Fc receptor system for monoclonal antibodies;

Animal models of disease that are thought to be similar to the human disease may provide further insight into pharmacological action and PK.

Therefore, in certain cases, studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals.

The scientific justification for the use of these animal models of disease to support safety should be provided.

Non-clinical studies in non-relevant species may give rise to misinterpretation and are discouraged.

The use of *in vitro* human cell systems could provide relevant additional information, especially for the translation of the mode of action from animal to human.



Qualitative and quantitative differences may exist in biological responses to a new IMP in animals compared to humans.

For example, there might be differences in affinity of the new candidate for molecular targets, but also physiological differences in tissue distribution of the molecular target, cellular consequences of target binding, cellular regulatory mechanisms, metabolic pathways, or compensatory responses to an initial physiological perturbation.



Where there is evidence of species-specificity of action from *in vitro* studies with human cells compared with cells from a test species, the value of the *in vivo* response of the test species may be significantly reduced in terms of predicting the *in vivo* human response.

It should be noted that a similar response in human and animal cells *in vitro* is not necessarily a guarantee that the *in vivo* response will be similar.



In practice this means that non-clinical studies with highly human-specific medicinal products may:

not reproduce the intended human pharmacological effect in animals;

give rise to misinterpretation of PK and PD results;

not identify relevant toxic effects.



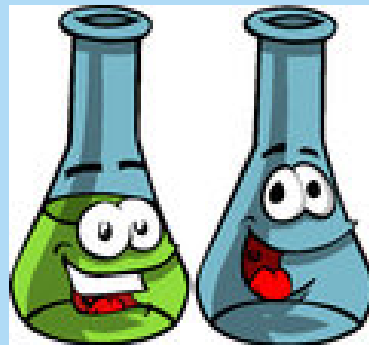
A weight-of-evidence approach should involve integration of information from *in vivo*, *ex vivo* and *in vitro* studies into the decision-making process.

High human-specificity of a medicinal product makes the non-clinical evaluation of the risk to humans more difficult, but does not imply that there is always an increased risk.



Secondary PD should also be critically evaluated and documented.

This might also include effects on other downstream or physiologically integrated endpoints.

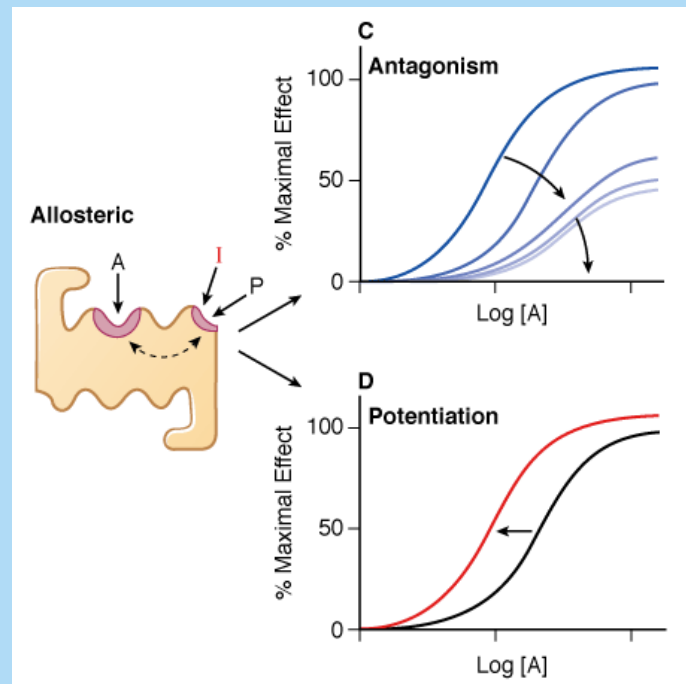


The primary and secondary PD should be conducted *in vitro*, using animal and human-derived material and *in vivo* using animal models, as relevant.

These studies should include target interactions preferably linked to functional response, *e.g.* receptor binding and occupancy, inhibition of enzymes, duration of effect and dose-response relationships.

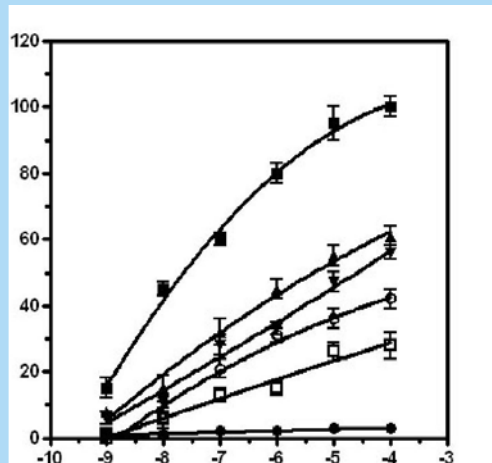


A dose/concentration-response curve of the pharmacological effect(s) should be established with sufficient titration steps to detect significant pharmacological effects with low doses and to identify active substances with U-shaped, bell-shaped or time dependant dose-response curves.



The usefulness of PD data following repeated dosing testing is often overlooked!

While single dose PD data can be used for an initial interpretation of the potential outcome of multiple dosing, consideration should be given to conducting repeated dose pharmacology studies or to include PD endpoints in repeated dose toxicity studies



The core battery of safety pharmacology studies includes the assessment of effects on cardiovascular, central nervous and respiratory systems, and should generally be conducted before human exposure, in accordance with ICH S7A and S7B.

When warranted, supplemental and follow-up safety pharmacology studies can be conducted during later clinical development.

Consideration should be given to inclusion of any *in vivo* evaluations as additions to general toxicity studies, to the extent feasible, in order to reduce animal use.

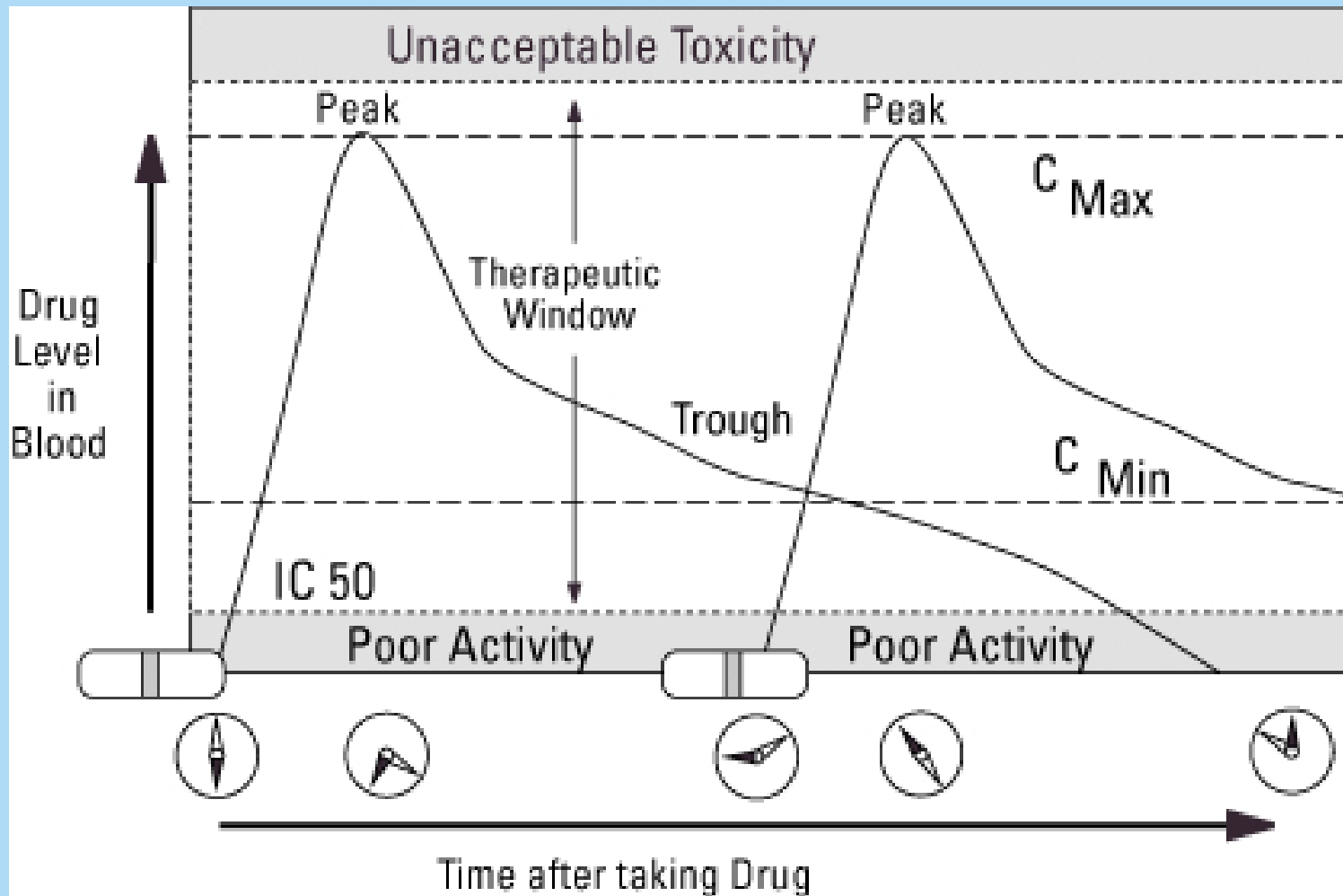
Pharmacokinetics

ICH Topic M 3 (R2)
Non-Clinical Safety Studies for the Conduct of
Human Clinical Trials and Marketing Authorization for Pharmaceuticals

ICH Topic S 3 A
Toxicokinetics: A Guidance for Assessing Systemic Exposure in Toxicology Studies

Guidance for Industry
Safety Testing of Drug
Metabolites

Guidance for Industry
Estimating the Maximum Safe
Starting Dose in Initial Clinical Trials
for Therapeutics in Adult Healthy
Volunteers



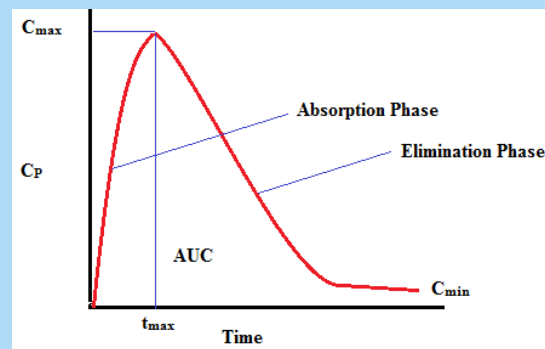
PK and toxicokinetic (TK) data should be available in ALL species used for the non-clinical safety studies conducted, and should adequately support the interpretation of data from *in vivo* PD models.

Sponsors must supply a brief summary of the analytical assays, and their limits of quantification, used to characterise the nonclinical PK and TK.

Systemic exposures at PD doses in the relevant animal models should be determined and considered especially when PD effects are suspected to contribute to potential safety concerns.

In vitro metabolic and plasma protein binding data for animals and humans and systemic exposure data in the species used for repeated-dose toxicity studies generally should be evaluated before initiating human clinical trials.

Further information on PK (e.g., absorption, distribution, metabolism and excretion), in test species and *in vitro* biochemical information relevant to potential drug interactions (including studies on transporters, CYPs *etc.*) should be available before exposing large numbers of human subjects or treating for long duration (generally before Phase III).



Problem Areas and How to Resolve Them



Scientific Advice!!





Risk comes from not knowing what you're doing!

Warren Buffett



The MHRA, and many other EU Member States, have, for many years, provided scientific and regulatory advice to sponsors.

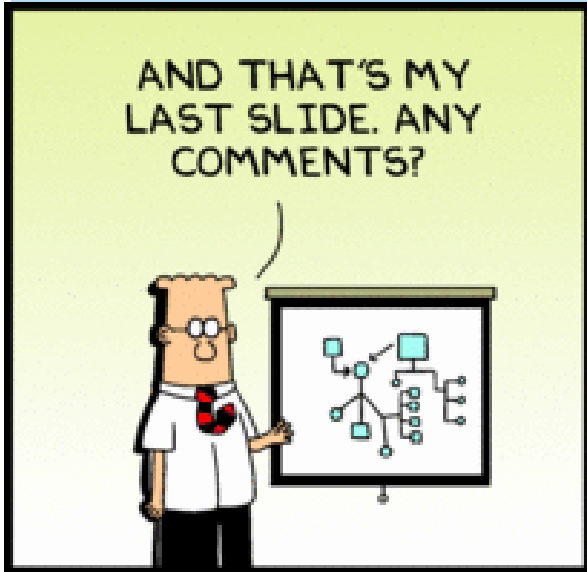
Scientific advice can be requested during any stage of the initial development of the medicinal product (before submission of a marketing authorisation application), and also during the pre-submission period for a variation to an existing marketing authorisation.

The European Medicines Agency (EMA) addresses the unique needs of micro, small and medium-sized enterprises (SMEs) through the SME office.

This dedicated interface has the sole remit of providing financial and administrative assistance to small pharmaceutical companies.



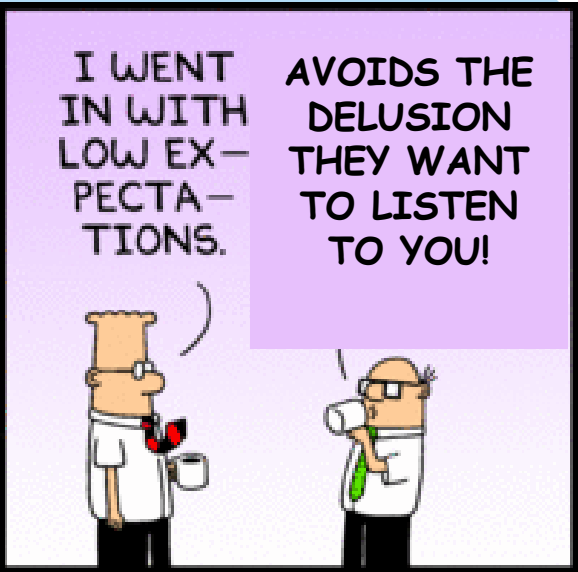
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



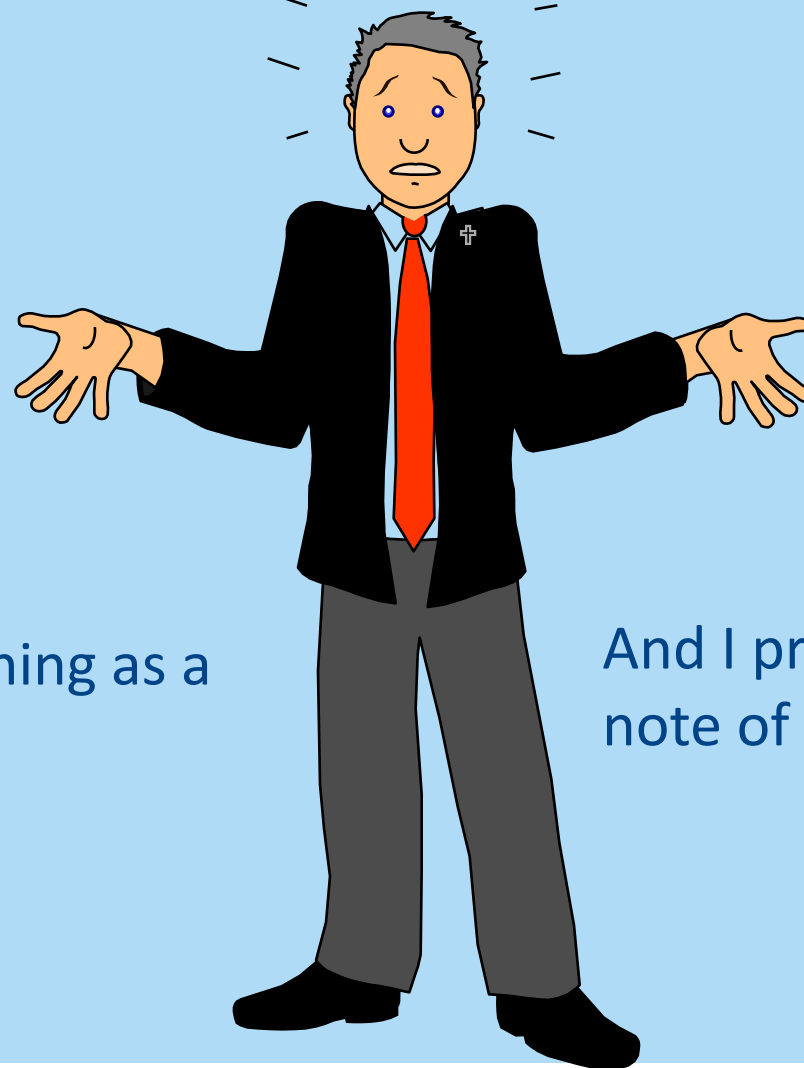
Dilbert.com DilbertCartoonist@gmail.com



©2011 Scott Adams, Inc. Dist. by Universal Uclick



Any Questions ?



Don't be shy!

There's no such thing as a silly question to a Regulator!

And I promise I won't take note of your names!!