

# Pharmaceutical development and quality assurance of FDCs

**Susan Walters B Pharm PhD**  
**Consultant and adjunct Associate**  
**Professor Faculty of Medicine,**  
**University of New South Wales**



## Abstract

- Therapeutic outcomes depend in part on product quality. This paper provides clinicians with a background to minimum quality standards.
- Good results in clinical trials can be repeated only if subsequent batches behave in the same way as those used in the trials. Consistent quality is essential between and within batches. It is not desirable to find out via a therapeutic failure that new batches of a product are of poor quality.
- Key factors influencing quality include:
  - Suitability of the formulation, including appropriate specifications for the finished product, ingredients and the container
  - A validated and controlled manufacturing procedure
  - Stability under the conditions of storage and for the duration of the claimed shelf life
  - Good and consistent bioavailability
- Preformulation studies based on scientific principles carry some cost but are rewarded by
  - Long term benefits for consistent quality and good patient outcomes, and
  - A much increased probability that the product will pass regulatory hurdles.
- Ongoing monitoring of product quality is essential, for example when new field storage conditions are envisaged or when changes to the product are inevitable following non-availability of ingredients, containers, sites of manufacture etc. Changes can alter product characteristics and must be validated according to the nature of the change. Validation of major changes may include new stability and/or bioavailability studies.
- In general, the more complex a product, the more that can go wrong and consequently the more effort must be put into specifying and controlling

ingredients, method of manufacture etc. Fixed-dose combinations are more complex than single entity products.

- There is already considerable experience with formulation and manufacture of FDCs and the problems that can arise for quality. New combinations are under development, with the potential for new problems in product quality. Without ongoing literature reviews, known problems may be repeated.
- Recommendations at the end of this paper are intended to facilitate the development and quality control of the FDCs that are the subject of this meeting.

## Introduction

The consequence for the patient of poor product quality can be therapeutic failure or toxicity. Some examples follow.

### *Low potency:*

- A WHO press release in November 2003 stated *inter alia*:
- "A recent WHO survey of the quality of antimalarials in seven African countries revealed that between 20% and 90% of the products failed quality testing. The antimalarials in question were chloroquine-based syrup and tablets, whose failure rate ranged from 23% to 38%; and sulphadoxine/pyrimethamine tablets, up to 90% of which were found to be below standard. The medicines were a mixture of locally produced and imported products" <sup>1</sup>
- Therapeutic failures in the Amazonian region have been attributed at least in part to poor and variable potency of antimalarial drugs<sup>2</sup> as assessed by chemical assay.
- It has been suggested that suboptimal potencies observed in chloroquine and amoxicillin products purchased in Nigeria are likely to be a factor in the selection pressure for drug-resistant organisms<sup>3</sup>.
- Samples of chloroquine, amoxicillin, tetracycline, co-trimoxazole and ampicillin-cloxacillin taken in Nigeria and Thailand had lower than expected potencies, and six samples of chloroquine had no detectable potency<sup>4</sup>.

### *Method of manufacture:*

- Variations in particle size, excipients or manufacturing process of the experimental preparations or capsules produced a marked change in bioavailability of rifampicin<sup>5</sup>.
- The order in which drugs were mixed during production had an "alarming" effect on bioavailability of rifampicin<sup>6</sup>.

- A change in the method of manufacture of carbamazepine tablets led to intoxication in some patients<sup>7</sup>.

**Excipients:**

- Formation of non-absorbable insoluble complexes between drugs and excipients is known for tetracyclines and dicalcium phosphate, amphetamine and sodium carboxymethylcellulose, and phenobarbitone and polyethylene glycol 4000<sup>8</sup>.
- Change of excipients in a formulation led to an outbreak of phenytoin intoxication in an Australian city<sup>9</sup>.
- Use of an excipient without prior information on its toxicology led to an outbreak of toxicity in Haiti<sup>10</sup>.

**Impurities:**

- Fever, tachycardia, hypotension and rigors occurring with once daily dosing of gentamicin were attributed to impurities from a particular supplier of the drug<sup>11</sup>.

**Stability:**

- Decomposition was the cause of a number (but not all) of the observed low potencies of antimalarial and antibiotics in Nigeria and Thailand<sup>4</sup>.
- Fanconi syndrome has been known to result from consumption of degraded tetracycline<sup>12,13</sup>
- Allergic reactions to penicillin are enhanced by formulations that encourage polymerization and reactions with certain carbohydrates<sup>14</sup>.

**Bioavailability**

- Therapeutic failures due to poor bioavailability are well known, for example to rifampicin<sup>15</sup>.
- Higher bioavailabilities of artemether and benflumetol were associated with improved parasitic clearance time and 28 day cure rate respectively<sup>16</sup>
- Different brands of rifampicin have been shown to have different bioavailabilities at the same dose<sup>17</sup>.
- The bioavailability of rifampicin is sometimes reduced when formulated in an FDC, but the effect is inconsistent<sup>18,19,20,21,22</sup>

## Preformulation studies

Once a formulation and method of manufacture have been developed, the temptation is to proceed with this design even if stability and/or bioavailability testing show that it is suboptimal. Probably at least a year will have passed by the time bioavailability studies are completed and stability studies produce meaningful long term results, during which time rival manufacturers will have been developing their own products. So how can a manufacturer increase the probability that a particular formulation will be successful in terms of consistent quality and regulatory compliance? Answer - by conducting a thorough review of relevant scientific literature and by undertaking preformulation studies.

Systematic *preformulation studies* on the active pharmaceutical ingredient (API) and on pilot formulations attempt to predict the viability of various formulations and methods of manufacture.

### **So what exactly are preformulation studies?**

Preformulation studies include studies of:

- The physicochemical properties of manufactured batches of the API, and an assessment of their relevance to the final formulation
- The chemical and physical stability of the API
- The impurity profiles of the API, including the typical content of synthetic by-products and degradation products
- Chemical compatibility of the active with potential excipients

These studies give clues as to how to achieve the desired performance of the finished product.

Even after developing a formulation and method of manufacture on these principles, it is still necessary to confirm stability and bioavailability, but there is a smaller probability that the formulation will fail. If two or three formulations are developed in parallel, there is an even greater probability that one will be successful. Whilst there are costs associated with preformulation studies, they significantly minimize the risks of failure and increase the likelihood of producing a high quality product.

### **Outcomes to be expected from preformulation studies**

The expected outcomes are that the product:

- Will deliver the drug to the site of action at the intended concentration.
- Will meet product specifications, including limits for content of drug and impurities, and suitable physicochemical tests such as dissolution rate, particle size of suspensions etc.
- Will be consistent from one dosage unit to another (eg tablet to tablet), from batch to batch, and from one manufacturing site to another. That includes consistent bioavailability.
- Will be chemically and physically stable for a suitable time period under convenient storage conditions. That is it continues to meet specifications.
- Can be manufactured at a cost that is consistent with the price that will be paid.
- As far as is possible, will be acceptable to the patient in terms of convenience and palatability.

### **Some specific benefits of conducting preformulation studies**

#### ***Setting specifications for the API***

With relevant *in vitro* information to hand, a manufacturer is in a better position to establish appropriate specifications for batches of the API so as to ensure an optimum and consistent performance for successive batches of the finished product.

***Minimising development costs***

By optimising the formulation before commencing costly bioavailability and bioequivalence studies, fewer such studies need be conducted.

***Avoiding failures during long-term stability***

Failure after say 2 or 3 years of long-term stability testing can set back a registration program significantly. Sound predictions as to the chemical and physicochemical stability of the active, and compatibility with excipients, other actives and the container, can minimize such failures.

***Minimizing the need for in vivo bioavailability/ bioequivalence studies***

FDA's ground-breaking development of the Biopharmaceutical Classification System<sup>23</sup> has narrowed the range of products for which bioavailability/ bioequivalence studies must be conducted. In particular, BCS class 1 drugs can now avoid (or obtain a waiver of) *in vivo* (bioequivalence) studies. In Australia (and probably in other countries too), a drug's BCS classification is taken into account when deciding whether or not a bioequivalence study is needed for a new product or a change to an existing product<sup>24</sup>.

Biopharmaceutical classification involves determining:

- 1 The solubility of the active itself in aqueous media of various pH, and
- 2 The ability of the active to cross the gut wall ('gastrointestinal permeability').

The more recent advent of 'biorelevant dissolution media' in an attempt to better predict *in vivo* dissolution rate has the potential to extend this waiver to BCS class 2 drugs. Dressman et al<sup>25,26</sup> developed a series of these media, with some success in predicting the *in vivo* behaviour of different formulations of BCS Class II drugs, and alteration of their bioavailability in the presence of food. With more development, these studies may provide a means of optimizing formulations of BCS Class 2 drugs without the need for bioavailability or bioequivalence studies. As defined by Dressman et al, 'biorelevant' dissolution media are of biological tonicity, pH and content of lecithin (mimicking bile salts). They attempt to reproduce conditions in the human stomach or proximal intestine.

***In addition, development of suitable assay procedures is critical at this stage,*** both to ensure that the results of assay, stability and bioavailability and bioequivalence testing are sound, and so as to ensure that results are credible at the later (and critically important) regulatory stage. For the purposes of quality control and stability testing, assays must be established for each active in the presence of the others, thus requiring additional validation for specificity. Validated and specific methodology is needed for assays of drugs in a biological fluid, usually plasma. The presence of more than one drug complicates assays, especially for bioavailability studies when multiple metabolites and sometimes degradation products are also present.

*Preliminary stability studies* involve chemical, physicochemical and, when necessary, microbiological tests.

Stability studies are sometimes thought of as concerning only chemical stability but the stability of physicochemical and microbiological characteristics are also important. These are some examples of non-chemical characteristics that can change on aging:

- Particle size of suspensions (often 'disproportionation', that is big particles get bigger and small particles get smaller)
- Polymorphic form of the active when the active is present in solid form, eg in tablets, capsules, and suspensions
- Dissolution rate of solid dosage forms
- Preservative efficacy of multidose suspensions, both sterile and non-sterile

Failure to control the first three of these may compromise the rate and extent of absorption of the active.

It probably goes without saying that in general stability is reduced at higher temperature. For some drugs, stability is also reduced at high humidity.

An issue that occasionally rears its head is the **acceptability of various excipients in different regulatory jurisdictions**. WHO's *Manual for a Drug Regulatory Authority* discusses internationally available lists of acceptable excipients for different routes of administration<sup>27</sup>. Many authorities are vague on this point, and it is probably less of an issue in countries that do not have a strong DRA.

## Some examples of the relevance of the properties of the API to product formulation!

### *Solubility*

- If water solubility is low, then the formulator will also examine:
  - The effect of solubilising agents on solubility. Selection of the optimum dissolution enhancer for a formulation can improve dissolution rate
  - The properties of solid dispersions of the drug. For example Abbott Labs have published information on the properties of ritonavir in solid dispersions<sup>28</sup>.

Formulation as soft gelatin capsules containing a fatty matrix is an alternative for low dose actives.

### *pKa*

pKa indicates how solubility will change with pH.

### *Polymorphic form*

If polymorphs of the active exist, it is important to ensure that batches of the API are always of the optimum polymorphic form. See below for more information and a relevant example.

**Bulk density**

<i>Hygroscopicity</i>	}	
<i>Flow properties</i>	}	These properties are important in designing a reliable manufacturing method
<i>Wettability / contact angles</i>	}	
<i>Compressibility</i>	)	
<i>Ability to maintain a static charge</i>	}	

*Taste/palatability* - Caution toxicity!

**Stability**

- The effect on the API of heat, light, moisture, oxidative conditions, and altered pH
- Compatibility of the API with potential excipients

**Polymorphic form**

Polymorphism is the ability of a substance to exist as more than one type of crystal, each crystal having a different internal arrangement of molecules. The different types of crystal can have different physicochemical properties such as melting point and, significantly for pharmaceuticals, the rate at which the substance dissolves in a solvent. Because biological environments are aqueous in nature, polymorphism is generally most relevant for drugs that have low water solubility and for which bioavailability may be dissolution-limited.

During chemical synthesis, the conditions of final purification (usually recrystallisation or slurring) largely dictate the final polymorphic form. The nature of the solvent and the rate and temperature of crystallisation are particularly important. Once the most suitable polymorph has been identified, purification conditions can be adjusted so as to produce it more reliably.

Some polymorphs are physically unstable and can metamorphose into another polymorph, thus providing a mechanism by which the dissolution rate of a finished product can change over time.

It is important to know the polymorphic forms in which a substance can exist, the stability of each, and how they can be distinguished during quality control, in order to ensure that the API (the raw material form of the drug) is always presented for use in manufacture in the most suitable polymorphic form.

In 1998, soft gelatin capsules containing ritonavir were found to have a poor dissolution rate and different to earlier batches<sup>29</sup>. Ritonavir has low water solubility and manufacture of capsules involves initial dissolution in ethanol followed by mixing with other excipients. Investigation showed that a hitherto unknown polymorph of even lower solubility than the only one previously known had formed in some batches of the capsule. Insidiously, once detected, polymorph #2 spread to batches of the oral solution, which could no longer be stored in a refrigerator without crystallising. The product was consequently reformulated.

## Good Manufacturing Practice (GMP)

Codes of GMP are now established internationally<sup>30,31,32</sup> and are recognised as an important means of controlling and improving pharmaceutical quality. Regulatory authorities conduct audits (or inspections) of pharmaceutical manufacturing premises within their jurisdiction and an 'acceptable' rating is a prerequisite to issue of a manufacturing licence. Authorities exchange information in the form of certificates of acceptability for various types of manufacturing, such as sterile products, solid oral dosage forms or APIs. Both the Pharmaceutical Inspection Cooperation Scheme<sup>31</sup> and the WHO Certification Scheme<sup>33</sup> exist to facilitate and promote such exchanges.

The underlying principles for GMP are these:

- Buildings used for manufacture must be suitable for the purpose.
- Staff must be qualified and experienced.
- There should be an effective system of quality assurance in place and fully functioning.
- Documentation trails should exist and should be readily accessible.

Quality assurance systems include comprehensive standard operating procedures and batch manufacturing instructions, which should be sufficiently detailed to ensure that all batches are manufactured in exactly the same way and result in a consistent product.

### **Issues that may arise in the formulation of FDCs that do not arise for single entity products include:**

- Possible chemical incompatibility between the drugs
  - At first manufacture
  - On aging
- Assay of multiple but similar components in a manner that is accurate, precise and specific

In the case of blister products that contain multiple products, control of manufacturing procedures must ensure that packs contain exactly what is intended and that there are no mix-ups. There is precedent for this type of product in 'sequential' oral contraceptives for which a single blister can contain up to four different types of tablet. Multiple containers in a single carton exist for triple combination therapy of gastric ulcers.

### **Chemical compatibility of drugs with excipients and with each other**

Some interactions are predictable given a good knowledge of organic chemistry, whilst others are not as obvious. If the nature of any interaction is known, conditions of manufacture can be adjusted to as to minimise its occurrence.

Some known interactions in the group of drugs of interest at this meeting include:

- **Acid/base interactions.** Sulphonamides are mildly acidic and can form salts with bases. An interaction between sulfamethoxazole and trimethoprim is known and has caused manufacturing problems for combinations of these drugs. Stability problems could also result in the form of altered dissolution rate on aging if a reaction occurs slowly. Other such interactions could occur under certain conditions, for example between sulfadoxine and pyrimethamine.
- **Schiff's base formation** occurs between primary amines and carbonyl-containing molecules. Flavouring agents commonly contain aldehydes and ketones that can potentially react with primary amines such as lamivudine, primoquine, trimethoprim and pyrimethamine.
- **When the primary amine component of a hydrazine reacts with a carbonyl group, the resulting compound is called a hydrazone.** This reaction is the basis of the reduced bioavailability of isoniazid in the presence of food.

Consequently carbonyl-containing excipients (such as reducing sugars and many flavouring agents) are best avoided in the formulation of drugs that contain primary amine and hydrazine moieties, including isoniazid, lamivudine, primoquine, trimethoprim and pyrimethamine.

- **The Maillard reaction and Amadori rearrangement** have been proposed in relation to pharmaceuticals, including fluoxetine<sup>34</sup> but, at least in that case, was not in practice a problem.

## Changes to registered products (variations)

Ongoing monitoring of product quality is essential. A product does not stand still; it changes over time. Not just in its stability, but in the materials and processes that contribute to manufacture. Perhaps the manufacturing equipment is replaced with something more modern? Or one of the ingredients is no longer available from the same supplier. Or the old pack size is no longer economically viable and marketing wants a pack that holds twice the quantity. Or storage conditions in the field are more extreme than was envisaged. Or the manufacturer wishes to extend the shelf life that was approved at first registration. The sponsor must ensure that there is no change to quality, safety or efficacy, including bioavailability. The key word here is validation. It must be demonstrated that changes/variations do not lead to a reduction in quality, either at batch release or on storage. Guidelines exist as to how to validate such changes<sup>35,36,37</sup>.

In addition, random postmarket testing by regulatory authorities is intended to (as we say in Australia) 'keep the bastards honest'. Targetted sampling is more efficient when a history is available for the type of product or for the manufacturer.

## Quality control of FDCs

Whilst, in most jurisdictions, manufacturers are not obliged to use the test methodology of the locally applicable pharmacopoeia, they do have to ensure that their products will meet that standard. Consequently when a pharmacopoeial monograph already exists for an FDC and its APIs, the task of the regulator in assessing a dossier and testing samples is simplified. The absence of monographs on a number of FDCs therefore means that regulatory agencies must commit more resources to assessment and testing, including often scarce technical skills.

Complexity of analyses increases with the number of active ingredients. However today's analytical procedures can cope provided they have been suitably validated. High pressure liquid chromatography (HPLC) is commonly the method of choice today, being relatively inexpensive and usually not complex. Suitable equipment and columns are now widely available, although this may be less true in developing countries. In relation to the International Pharmacopoeia, the Essential Drugs and Medicines Policy team at WHO has stated:

*"Whenever possible, classical procedures are used in the analytical methods so that the pharmacopoeia can be applied without the need for expensive equipment. In addition, alternative methods have been introduced for use whenever a more complex method is suggested."*<sup>38</sup>

Validation of HPLC methods is called *system suitability testing*. Contrary to popular opinion, an HPLC method is not always specific for the target analyte. Methods should be tested in the presence of known and likely contaminants, and refined as necessary. Note also that a long retention time does not in itself guarantee that an assay will separate the target analyte from related substances.

In an unpublished and confidential report to WHO, Wieniawski has reviewed analytical specifications for the antiretroviral and antimalarial combination products that were assessed during the WHO pilot project on drug procurement and sourcing<sup>39</sup>. Some of the following comments address issues raised in that report.

### Availability of reference standards for quality control

To allow for variation in the conditions under which an analysis is conducted, assay of a test sample is always conducted in parallel with an identical assay of a standard reference substance that has a nominal 100% response. This is true for assays of the active and of impurities in APIs and finished products, and during dissolution studies. Assays of unknown impurities, or of impurities present in very small proportions, are sometimes conducted without a reference standard and these are termed *semiquantitative* assays.

Availability of reference standards is then an important factor in conducting meaningful quality control. Reference standards are not available for all of the

actives under consideration at this meeting. Even when they are available, there is often a substantial cost. For example, reference standards provided by the United States Pharmacopeia can be at a significant cost because companies based in the USA can afford those prices.

### **Specifications at batch release and throughout the shelf life ('expiry' limits)**

Although many companies resist, DRAs should seek tighter limits at release than at expiry, especially for drugs that show chemical or physicochemical instability. This provides a margin of patient safety in the event of instability and interlaboratory variation.

### **Monographs on individual APIs**

It is preferable, but not an absolute requirement, that monographs on individual APIs be available before a monograph is published on an FDC containing those APIs. I do not believe that monographs on single component dosage forms need be available prior to monographs on FDCs.

### **Impurities**

A degree of contamination with impurities is an inevitable result of chemical synthesis and, in some cases, instability of the active ingredient or interaction with excipients. The responsibility of the regulator is to ensure that active ingredients are as pure as is consistent with patient safety and the economic viability of the product.

Wieniawski suggests<sup>39</sup> that separate tests for impurities are not necessary because limits can be incorporated into an HPLC assay procedure for the active. This may often be true but only if the assay procedure has been validated for the impurities in question. HPLC assays are often conducted with short retention times to allow fast laboratory throughput and may not be capable in that form of separating and quantifying (or semiquantifying) impurities.

It is not necessary to identify impurities or degradation products in active ingredients and finished products if they are present below threshold concentrations that depend on the daily dose of the active<sup>40,41</sup>.

### **Registration 'packages'**

Networks exist internationally amongst generic manufacturers for the sale of complete registration 'packages'. These comprise a complete registration dossier including formulation, method of manufacture (with in-process controls and limits), quality control methodology and specifications, and the results of stability and bioavailability studies. Whilst some adaptation may be necessary for certain jurisdictions, the package is often acceptable to even relatively advanced regulatory authorities.

WHO may wish to consider purchasing, or even commissioning, regulatory packages for FDCs that could be made available free of charge in less well-resourced nations. The economics of such a strategy would have to be carefully considered.

## Recommendations

The following recommendations are intended to facilitate the development and quality control of the FDCs that are the subject of this meeting. They are not necessarily listed in order of priority.

### *Pharmaceutical development*

- 1 Publish formulations and methods of manufacture for the FDCs in question.
- 2 Consider the possibility of WHO purchasing a registration package for a generic and making it publicly available. Such a package would include inter alia formulation, method of manufacture (with in-process controls and limits), methods of QC testing and limits, stability data, bioavailability data.
- 3 Publish preformulation information on the drugs in question, including information on stability. The format of the series *Analytical profiles of drugs substances and excipients*<sup>42</sup> could serve as a model.
- 4 Determine whether the Biopharmaceutical Classification System<sup>3</sup> can reliably be applied to FDCs. If yes, then ascertain the GI permeability of the drugs in question.

### *Quality control*

- 5 Develop and publish monographs on the individual APIs and finished products in question where these do not already exist.
- 6 Ensure that reference standards are available for the drugs in question, and at a price that is acceptable to the manufacturers and the regulatory authorities involved.

## References

- 1 WHO: World Health Organization steps up action against substandard and counterfeit medicines; Asian and African Countries Move to improve the quality of their medicines. Press release 11/11/03.  
<http://www.who.int/mediacentre/releases/2003/pr85/en/>
- 2 Petralanda I: Quality of antimalarial drugs and resistance to Plasmodium vivax in Amazonian region. *Lancet* 345(8962):p1433, 1995
- 3 Taylor RB, Shakoob O, Behrens RH: Drug quality, a contributor to drug resistance? *Lancet* 346(8967):p122, 1995

- 4 Shakoor O, Taylor RB, Behrens RH: Assessment of the incidence of substandard drugs in developing countries. *Tropical Medicine & International Health* (9):839-845, 1997
- 5 Buniva G, Pagani V, Carozzi A: Bioavailability of rifampicin capsules. *International Journal of Clinical Pharmacology & Therapeutic Toxicology* 21(8):404-409, 1983
- 6 Fox W: Drug combinations in the bioavailability of rifampicin. *Tubercle* 71: 241-245
- 7 Eadie MJ, Hooper W: Intermittent carbamazepine intoxication possibly related to altered absorption characteristics of the drug. *Medical Journal of Australia* 146(6): 313-6, 1987
- 8 Ashford M: Bioavailability - physicochemical and dosage form factors. In *Pharmaceutics, the science of dosage form design*, 2nd edition, Churchill Livingstone, 2002
- 9 Tyrer JH, Eadie MJ, Sutherland JM, Hooper WD: Outbreak of anticonvulsant intoxication in an Australian city. *British Medical Journal* 4(730):271-3, 1970
- 10 O'Brien KL, Selanikio JD, Hecdivert C, Placide MF, Louis M, Barr DB, Barr JR, Hospedales CJ, Lewis MJ, Schwartz B, Philen RM, St Victor S, Espindola J, Needham LL, Denerville K: Epidemic of pediatric deaths from acute renal failure caused by diethylene glycol poisoning. Acute Renal Failure Investigation Team. *Journal of the American Medical Association* 279(15):1175-80, 1998
- 11 Fisman DN, Kaye KM: Once-daily dosing of aminoglycoside antibiotics. *Infectious Diseases Clinics of North America* 14(2):475-487, 2000
- 12 Mull MM: The tetracyclines: a critical appraisal. *Am J Dis Child* 11:483-493, 1966
- 13 Herxheimer A: Principles of Clinical Pharmacology, in *Oxford Textbook of Medicine* 4th edition, Oxford University Press, 2003
- 14 Bungaard H: Pharmaceutical aspects of penicillin allergy: polymerization of penicillins and reactions with carbohydrates. *J Clin Hosp Pharm* 5:73 1980
- 15 Van Crevel R, Alisjahbana B, De Lange WCM, Borst F, Danusantoso H, Van der Meer JWM, Burger D, Nelwan RHH: Low plasma concentrations of rifampicin in tuberculosis patients in Indonesia. *International Journal of Tuberculosis & Lung Disease* 6(6):497-502, 2002
- 16 Ezzet F, Mull R, Karbwang J: Population pharmacokinetics and therapeutic response of CGP 56697 (artemether + benflumetol) in malaria patients. *British Journal of Clinical Pharmacology* 46(6): 553-561, 1998
- 17 Garg SK, Chakrabarti A, Panigrahi D, Sharma M, Talwar P, Kumar N, Sharma PL: Comparative bioavailability & in vitro antimicrobial activity of 2 different brands of rifampicin. *European Journal of Drug Metabolism & Pharmacokinetics* 16(3):223-229, 1991
- 18 Pillai G, Fourie PB, Padayatchi N, Onyebujoh PC, McIlleron H, Smith PJ, Gabriels G: Recent bioequivalence studies on fixed-dose combination anti-tuberculosis drug formulations available on the global market. *International Journal of Tuberculosis & Lung Disease* 3(11):S309-316,1999
- 19 Doshi BS, Bhate AD, Chauhan BL, Parkar TA, Kulkarni RD: Pharmacokinetic interaction of oral rifampicin & isoniazid in normal subjects. *Indian Drugs* 23(12):672-676, 1986
- 20 Ellard GA, Ellard DR, Allen BW, Girling DJ, Nunn AJ, Seng-Kee T, Tiong-Har T, Hin-Kwong N, Siu-Lun C: The bioavailability of isoniazid, rifampicin, and pyrazinamide in two commercially available combined formulations designed for use in the short-course treatment of tuberculosis. *American Review of Respiratory Disease* 133: 1076-1080, 1986
- 21 Panchagnula R, Kaur K, Singh I, Kaul CL: The WHO simplified study protocol in practice: investigation of combined formulations supplied by the WHO. *International Journal of Tuberculosis & Lung Disease* 3(11):S336-342, 1999

- 22 Gurumurthy P, Ramachandran G, Vijayalakshmi S, Hemanth Kumar AK, Venkatesan P, Chandrasekaran V, Vjayasekaran V, Kumaraswami V, Prabhaker R: Bioavailability of rifampicin, isoniazid & pyrazinamide in a triple drug formulation: comparison of plasma & urine kinetics. *International Journal of Tuberculosis & Lung Disease* 3(2):119-125, 1999
- 23 FDA: Waiver of in vivo bioavailability & bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system, in, 2000
- 24 McLachlan A: Personal communication
- 25 Dressman J, Reppas C: In vitro-in vivo correlations for lipophilic, poorly water-soluble drugs. *European Journal of Pharmaceutical Sciences* 11:S73-S80, 2000
- 26 Kostewicz E, Brauns U, Becker R, Dressman JB: Forecasting the oral absorption behavior of poorly soluble weak bases using solubility & dissolution studies in biorelevant media. *Pharmaceutical Research* 19:345-349, 2002
- 27 WHO: Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: A manual for a drug regulatory authority, 1999
- 28 Law D (Abbott Laboratories): Physicochemical considerations in the preparation of amorphous ritonavir-poly(ethylene glycol) 8000 solid dispersions. *Journal of Pharmaceutical Sciences* 90:1015-1025, 2001
- 29 Bauer J, Spanton S, Henry R, Quick J, Dziki W, Porter W, Morris J: Ritonavir: An extraordinary example of conformational polymorphism. *Pharmaceutical Research* 18:859-866, 2001
- 30 WHO: Good Manufacturing Practices for pharmaceutical products: Main principles. Annex 4 in *WHO Technical Report Series* No. 908, 2003
- 31 Pharmaceutical Inspection Cooperation Scheme: Guide to good manufacturing practice for medicinal products. September 2003 (<http://www.picscheme.org/docs>)
- 32 The Commission of the European Communities: Medicinal products for human and veterinary use; Good manufacturing practices. October 2003.
- 33 WHO: Guidelines for implementation of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce. Annex 10 in *WHO Expert committee on specification for pharmaceutical preparations*, 34th report, Geneva 1998
- 34 Wirth DD, Baertschi SW, Johnson RA, Maple SR, Miller MS, Hallenbeck DK, Gregg SM: Maillard reaction of lactose and fluoxetine hydrochloride, a secondary amine. *Journal of Pharmaceutical Sciences* 87:31-39, 1998
- 35 Food & Drug Administration: Guidance for Industry, Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products. FDA July 1997
- 36 Therapeutic Goods Administration: Changes which may be made to Pharmaceutical Aspects of Drug Products without Prior Approval (\*Self-Assessable Changes). Appendix 8 in *Australian Guidelines for the Registration Of Drugs: Volume 1, Prescription and other specified drug products*. TGA 1994
- 37 European Commission: Chapter 5 'Variations'. In Volume 2, *Pharmaceutical legislation : Notice to Applicants, Volume 2A - Procedures for marketing authorisation*. Date unclear.
- 38 WHO (EDM): The International Pharmacopoeia, 2003
- 39 Wieniawski W: Review of analytical specifications used in quality evaluations of antiretroviral and antimalarial combination products. *WHO unpublished*, 2003
- 40 ICH: Impurities in new drug substances (revised), <http://www.ich.org>, 2002
- 41 ICH: Impurities in new drug products (revised), [www.ich.org](http://www.ich.org), 2003
- 42 Various authors: *Analytical profiles of drug substances & excipients*, Academic Press, Various dates of publication