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Cover: Differential Scanning Calorimeter. Courtesy of APM Testing www.apmtesting.com (see page 8)

EDITORIAL COMMENT

Dear Colleagues

The new year has started and it is time for the latest issue of the EIPG-sponsored *European Industrial Pharmacy* journal which we take great pride in offering to our members across Europe.

The EIPG believe in representing the voice of 'grass roots' Pharmacists working in the Industry and to provide a resource for Pharmacists to ask for advice with respect to careers, education and continuing professional development. The EIPG is one of the few truly European Associations that is dedicated solely to the Industrial Pharmacist. In fact this is such a distinguishing feature, that I feel it should be repeated i.e. *EIPG is dedicated solely to promote, safeguard, and develop the interests of Industrial Pharmacists throughout Europe*. Each member of the Bureau is passionate in this respect and often spend 3 many hours of their own personal and family time with this goal in mind.

I am proud to be President of EIPG and to have such a dedicated team of Pharmacy Professionals working within the Bureau and throughout the General Assembly who want to see Pharmacists continue to enter this sector of practice.

We recently polled our members to find out what they wanted from the EIPG in the light of the significant changes ongoing in this sector.

Responses received were mainly from production, quality assurance and regulatory affairs staff and from Sweden research and development and regulatory affairs staff.

The order of priority of activities that individual members considered to be "Very/Fairly Important" was as follows:

1. EIPG representation of professional industrial pharmacy at meetings with the European Commission, EMA, EFPIA and European Schools of Pharmacy

2. Development of standards for CPD (Continuing Professional Development)

3. EIPG Publication of Codes and Standards for industrial pharmacy practice

4. Provision of a forum for job vacancies and careers advice to students and young pharmacists

5. To provide the opportunity for members to input their opinions on draft EU guidelines

6. Provision of career development advice

7. Provision of distance learning materials

8. Development of discussion groups with moderators

9. Reduced registration fees at national meetings arranged by any other national Association in Europe

The findings clearly show that our members felt that active dialogue with European Commission, Trades Associations, Regulatory Agencies and responses to the various directives were very important. In some ways these findings are most reassuring in that they align very neatly with our activities and strategy over the last 12 months as evidenced with our interactions with EMA Interested Parties meetings, EFPIA, the Commission, EAHP and PGEU.

These are interactions which EIPG will continue to pursue and lobby on areas such as maintaining Professional Standards, ensuring Patient Safety and Educational Standards.

As always, we remain open to suggestions and areas of focus going forwards into 2011 and individuals can contact me, my Executive Director Mrs Jane Nicholson or any member of the EIPG Bureau through accessing the EIPG website at www.eipg.eu

Best wishes

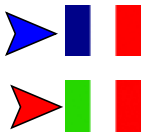
Dr Gino Martini FRPharms
EIPG President

SOLID ORAL DOSAGE FORMS FOR CHILDREN –

formulations, excipients and acceptance issues

by Ines Stoltenberg[*1], Gesine Winzenburg[2], Jörg Breitkreutz[1]*

The development of a drug product for the paediatric population has its specific challenges. The selection of the route of administration and the dosage form has to integrate therapeutic considerations, drug substance properties, technical feasibility and, above all, patient needs . Excipients require special scrutiny since tolerability in the paediatric population might be critical even if considered to be safe in adults due to the physiological differences.[1] The oral route of administration is the preferred one for children with liquid forms being favoured even though they are associated with some disadvantages, especially an unpleasent taste[2]. Recently, the World Health Organization (WHO) therefore stressed the advantages of the solid dosage forms versus the liquid forms for the oral route of administration[3]. This article reviews solid oral dosage forms marketed for children and discusses their age-appropriateness and the suitability of the excipients used.



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Excipients in paediatric medicines

Excipients are designated as inactive ingredients in medicines and should be safe for human use. However, excipients which are safe in adults could be critical for children, especially in newborns and infants due to their physiological characteristics and age-dependent maturation of organ function[2,4].

The EMA requires that excipients should be selected for the paediatric subpopulation with special care[5]. Often the use of solvents and surfactants is required to solubilise a poorly soluble drug. The addition of a buffering system, antioxidants, suspending agents and preservatives might be necessary to ensure stability. Flavours, sweeteners or polymers for film coating may be required to mask the unpleasant taste. For aesthetic reasons colouring agents might be used. Limitations in the type and amount of excipient often trigger a benefit- risk assessment.

The 'Acceptable Daily Intake' (ADI), a value established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is measured as the tolerated mass of excipient per body weight per day (in mg/kg/d)[6]. A similar approach is the estimation of the 'Permitted Daily Exposure' (PDE) for solvent residuals. Both ADI and PDE are commonly used for risk assessment of excipients in paediatric formulations. However, it should be kept in mind that the paediatric population shows particular differences from the 'normal' adult patient.

The ADI values of commonly used excipients in paediatric solid oral dosage forms are shown in **Table 1**. Critical excipients for paediatric subpopulations have been described by Breitkreutz and Boos in 2007[7]. Focusing on solid oral dosage forms, sweeteners such as aspartame, fructose, lactose, sorbitol and sucrose could cause toxicity problems for patients with metabolic disorders such as phenylketonuria, hereditary fructose intolerance and lactose intolerance. Hypersensitive patients could have problems with azo dyes, which are commonly used as colourants, causing allergies, urticaria, bronchoconstriction and angio-oedema.

Some solid oral dosage forms

Dispersible tablets

Dispersible tablets disintegrate in water within three minutes into a palatable solution or suspension. They can be manufactured by using standard technology and no special packaging is required.

A recent example of a successful paediatric formulation, fulfilling the recommended criteria for paediatric medicine, is Coartem® Dispersible (Novartis). The dispersible tablet is particularly suitable for infants and children from 5 kg to 35 kg. The tablet disintegrates in water into a pleasant-tasting suspension.
Excipients and their levels in the formulation were selected according to their ADI if available. For example, the level of sodium saccharin, a potent

Table 1.

Excipients in solid dosage forms		ADI[1] (mg/kg/day)	Warning/Restriction
Diluent	Corn starch	Not specified	None
	Microcrystalline cellulose	Not specified	Intestinal absorption, long term effect not known, should not be used for children ≤2y
	Mannitol	Not specified	None
	Lactose	Not specified	Lactose intolerance, galactosaemia
Sweetener	Sucrose	Not specified	Cariogenic
	Xylitol	Not specified	Well tolerated, suitable for patient with diabetes
	Saccharin	5	Carcinogenic potential (banned in Canada)
	Sucralose	15	None
	Aspartame	40	Phenylalanine source, Phenylketonuria
	Cyclamate	11	Unconfirmed carcinogenic potential (banned in US, permitted in Europe & China)
	Acesulfame	15	None
Surfactant	Polysorbate	10	None
Flavour	Flavouring agents	-	Allergenic potential, should not be used for children
Colourant	Azo dyes	2.5	Allergenic potential, should not be used for children
Lubricant	Magnesium stearate	Not specified	None
Coating	Modified celluloses	Not specified	None

[1] "not specified" describes a substance of very low toxicity, in the opinion of the Joint FAO/WHO Expert Commitee on Food Additives (JECFA). For that reason, the establishment of an acceptable daily intake is not considered necessary.[2]

sweetener, is below the ADI of 5mg/kg/d. The selection of flavour was based on a palatability study in 7-10 year-old African children.

There are several dispersible tablets marketed for children. Sinupret® Liquitabs® (Bionorica) contains three different flavours (strawberry, condensed milk and vanilla) and two sweeteners (aspartame and sodium cyclamate) to mask the bitter taste of gentian, the active ingredient. Sodium cyclamate has the lowest sweetening potency of the intense sweeteners, but combined with aspartame, a synergistic effect is achieved[8]. Even though results from carcinogenicity studies with sodium cyclamate have shown no evidence of an association with cancer in humans[9], this sweetener is banned in the US[10]. The product also contains propylene glycol which possesses a negative concentration-dependent risk assessment for oral use in children[4].

Multiparticulates

Multiparticulate formulations contain small particles with a diameter typically less than two millimetres (eg. granules or pellets). They can be easily administered either directly into the mouth or by mixing with food. Taste masking and modified release of multiparticulates are feasible by different technologies. Dosing flexibility and the possibility of combining several drug substances are further advantages.

An example is Artequin™ Paediatric (Mepha). The product is suitable for children with a body weight of 10-20kg. Pellets with a diameter of 0.5-1.5mm are provided in stick packs and can be applied directly into the mouth. To improve the palatability, sodium cyclamate (ADI 11mg/kg/d), saccharin sodium (ADI 5mg/kg/d) and xylitol are used. Xylitol is considered safe for children and is therefore a recommended sweetener[4].

Medikinet® (Medice) is used for children 6 years and older. Half of the pellets are coated with a polymethacrylate to achieve a modified drug release. However, an ADI for polymethacrylate derivates has not yet been determined[4]. Cases

of fibrosing colonopathy in children have been reported for pancreatic enzyme formulations coated with a methacrylic acid and ethylacrylate copolymer[11].

An innovative approach to administer multiparticulates is the dose-sipping technology (Grünenthal). Here the required dose of enteric-coated micro-pellets made from Tκ-carrageenan is filled into a drinking straw. An oral suspension is formed *in situ* by drinking a beverage of the patients' choice using the straw. Tκ-carrageenan is listed on the GRAS – list of the US Food and Drug Administration. The list contains food additives which are 'Generally Recognized As Safe' under the intended conditions of use[12]. But, like the ADI value, this is not thoroughly transferable to paediatric medicines.

Mini-tablets

Mini-tablets are less than 3mm in diameter[13]. They are easy to swallow, the taste can be easily masked with a coating and allow flexible dosing. State of the art compression technology is used in their manufacture.

Recently, an acceptability study demonstrated that pre-school children are able to swallow 3mm mini-tablets with some water[14].

Commercial mini-tablets for young children are Lamisil® Oral Granules (Novartis) and Orfiril long® 150mg (Desitin). Both products contain mini-tablets of approx. 2mm in diameter, predispensed in stickpacks and capsules. They are recommended to be administered by sprinkling on soft food.

Orally disintegrating tablets and lyophylisates

Orally Disintegrating Tablets (ODTs) disintegrate in the mouth in typically between 5 and 30 seconds without the need for water. This attribute overcomes the swallowing difficulties experienced with standard tablets and capsules and makes them suitable for children provided the formulation tastes good.

There are several commercial ODTs available for children. Ondansetron ratiopharm® ODT (ratiopharm) is one of them. The product is indicated for children over 2 years and contains tolerable excipients for this population, such as microcrystalline cellulose and mannitol (**Table 1**).

Lyophilisates, produced by freeze-drying, disintegrate quickly in the mouth, although they are sensitive to moisture and are easily crushed. Therefore a special packaging technology (peel-off blister) is required.

Zofran® 4mg Zydis lingual ODT (GlaxoSmithKline) is indicated for children over 2 years. The formulation contains one flavour (strawberry) and one sweetener (aspartame) to achieve an acceptable taste. However, it also includes methyl and propyl paraben as preservatives. For parabens the JECFA established a group ADI of 10mg/kg/d. In 2004, propyl paraben was excluded from the group ADI due to its estrogenic effects. Furthermore, in 2005, propyl paraben was placed on the priority list for toxicological re-valuation[15].

Chewable tablets and chewing gums

Chewable tablets can be chewed before swallowing and can be taken without water. They are palatable, stable, portable and well-tolerated by children ≥2y[11].

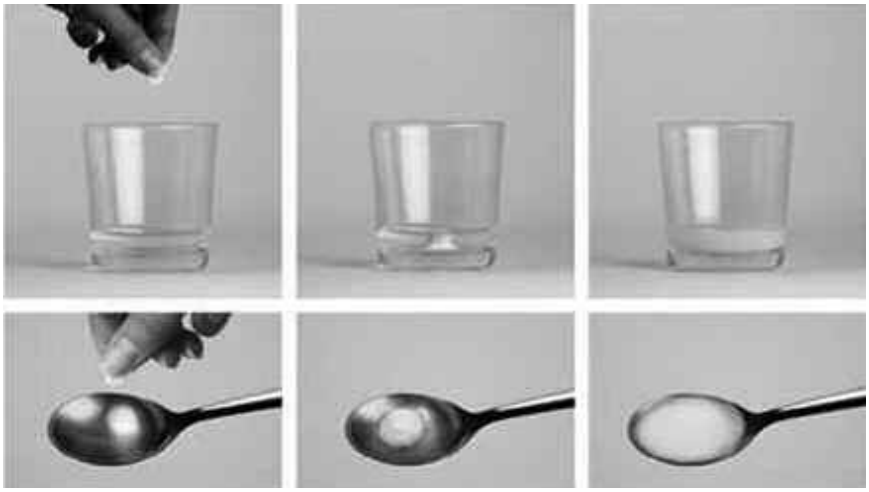
Singulair 4mg® Chewable tablets (Merck Sharp & Dohme) are suitable for children ≥4y. The product contains only few and non-critical excipients and has a palatable taste. Chewable tablets create new challenges in achieving taste-masking. Simple taste-masking approaches applicable for adults, such as the use of ion resins or cyclodextrines, may not be acceptable for children.

Zyrtec® chewable tablets (Pfizer) for children above 2 years, contains cyclodextrins either for solubilisation or taste-masking. ß-cyclodextrin is considered to be safe for oral use (ADI 5mg/kg/d) but the experiences with cyclodextrins in children is still limited.

Chewing gums are feasible for local and systemic treatment. Usually it takes 10-20 minutes to ensure the complete release of the dose. Gums are not intended to be swallowed and thereby are likely to be acceptable for children above 6 years. Superpep® Travel gum (Hermes) is a product for children ≥6y. The list of ingredients is extensive including four sweeteners (sorbitol, sucrose, aspartame and sodium saccharin) to cover the taste over the entire chewing time.

Oral wafers

Oral wafers, or orodispersible strips, are thin films of typically 2-8cm2 area and 20-500 µm thickness, containing typically ≤50mg of API. They are administered directly on the tongue. Wafers can dissolve or disintegrate in the mouth within a few seconds without water. Spitting out is very unlikely due to the immediate disintegration and the adherence to the mucosa. To date few OTC products are commercially available for pre-school children, eg. in USA as Triaminic® Thin Strips™ Cough & Runny Nose (Novartis Consumer Health). The products, intended for children ≥4y, contain several excipients, such as film-forming agents derived from cellulose and starch, as well as sweeteners, flavours, colouring agents and traces of class 3 residual solvents used as processing aids, far below the limits



accepted by Health Authorities (ICH guidelines). As this delivery form has to be well protected from ambient humidity, strips are usually provided as unit doses in child-proof pouches.

Recently, Setofilm® (Ondansetron 4 & 8mg) was approved in Europe as the first prescription-only oral wafer (Applied Pharma Research & Labtec & MonoSol Rx) for use in children from 6 months onwards.

"Special" formulations

Gummy bears (eg. Pedia Lax®, Fleet) and lollipops (eg. Get Better Bear®, Helms candy) are examples of special oral formulations. The gummy bears are for children above 2 years, whereas the lollipop is indicated for children above 3 years. They are attractive to children, taste sweet and hence help parents to administer the medication to their children.

The lollipop format is especially trendy in US compounding pharmacies. Lollipops are formulated according to individual taste preference.

However, these "special" formulations are not "sweets" and should be securely stored out of reach of children.

Conclusion

Various innovative solid dosage forms exist or are under development for paediatric use. They have the advantage over liquid oral dosages forms as they are compact, taste-masked and stable. They are potentially suitable for children but the acceptability of these dosage forms still needs to be demonstrated especially in the younger paediatric population. Excipients and their concentrations have to be limited in paediatric formulations, since excipients cannot be considered as inactive ingredients and safe for all paediatric subpopulations. However, there is still a lack of guidance, especially on quantitative aspects and on excipient acceptability for paediatric age groups. The EU regulation on Medicinal Products for Paediatric use, which came into force in the EU in 2007, and recent research will help provide access to better medicines for children in the future.

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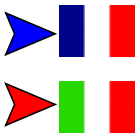
THE ROLE OF CALORIMETRY

in the development of drug delivery systems

by Simon Gaisford

Calorimetry is a wonderful analytical tool, because the property it measures (heat) is ubiquitous. Since virtually any process will occur with a change in heat content, virtually any process is open to calorimetric investigation. Whether calorimetry is a suitable tool to investigate a particular sample can be decided by sensitivity, sample size and data complexity.



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Heat as a marker of change

Sensitivity

It is impossible to anticipate the sensitivity of a calorimetric measurement for a particular sample unless the change in heat content (ΔH) for the measured process is known. The larger the ΔH value the more sensitive the measurement.

Sample size

Sample size is often a crucial consideration for pharmaceuticals where only a few milligrams of a material may exist. Most differential scanning calorimeters (DSC) utilise sample masses of ca. 2-5mg. Instruments such as isothermal or solution calorimeters, the main focus of this discussion, require larger masses, ca. 50-100mg (although these may be reduced if the ΔH value is high). Sample mass is also critical where the substance to be analysed is present in dilute concentration (such as a solution or powder blend) because the number of molecules of the substance can be low, even if the sample is relatively high. This led to the development of large volume DSC instruments used primarily for studying dilute solutions of macromolecules (polymers and biologicals). The fact that isothermal and solution calorimeters utilise large sample masses is in fact, an advantage when using calorimetry to study formulations. As noted above, the ability to study complex, heterogeneous samples is a strong asset and is no problem if the whole sample fits within the calorimetric ampoule. If this is not the case, then a representative fraction of the sample can be loaded instead.

Data complexity

The issue of data complexity is more fundamental and is one of the factors that has limited the more widespread application of calorimetric apparatus. Whereas spectroscopic data are resolved into intensities at specific wavelengths and it is possible to identify and quantify specific species in mixed samples. Heat does not come in different colours and so one measures the net change in heat content from all the processes that have occurred in the sample ampoule. The challenge lies in separating the data into their component parts and in ensuring that careless experimental design or analysis does not result in misinterpretation[1].

Operating principles

Calorimeters can be classified as temperature scanning or isothermal but share common measurement principles.

Measurement

There are only three methods by which heat can be experimentally measured:

- measurement of the power required to maintain isothermal conditions in a calorimeter, (power-compensation calorimetry)
- measurement of a temperature change in a system, multiplied by an experimentally determined constant (adiabatic calorimetry)
- measurement of a temperature difference across a path of fixed thermal conductivity, multiplied by an experimentally determined cell constant (heat-conduction calorimetry)

Note that all calorimetric measures therefore require a minimum of two experiments (one for measurement and one for calibration).

Differential scanning calorimetry

The most commonly encountered form of calorimetry, certainly in pharmaceutics, is differential scanning calorimetry (DSC). For this, the power output form a sample is measured, relative to an inert reference, as

it is heated or cooled in accordance with an underlying temperature programme.[2,3] DSC data can be presented in a number of ways; most commonly is plotted versus temperature although it is also common to plot heat capacity versus temperature[4]. It is also possible to increase the sample temperature in defined steps, so termed 'step-isothermal'.

Isothermal calorimetry

In isothermal calorimetry (IC), data are recorded as the sample is held at a constant temperature. In the simplest cases, sample and reference materials are placed in sealed ampoules which can be re-usable or disposable, can vary in volume and can be constructed from a variety of materials (typically glass or metal). In batch calorimetry the reaction vessel is divided into two compartments, connected by an air-space. Each compartment can be separately charged with sample (either a solid or a liquid). Once thermal equilibrium has been attained, the contents of the two compartments are mixed, usually by rotating the vessel, and the heat of interaction is measured. Batch calorimeters are also known as mixing calorimeters.

The versatility of isothermal calorimeters derives from the many ways of loading the sample in the ampoule and controlling the local environment, such as the relative humidity (RH) in the ampoule.

Applications to formulation

Compatibility screening

One primary concern early in the formulation process is to ensure there are no incompatibilities between the active pharmaceutical ingredient (API) and any of the excipients. Usually binary mixtures of the active and each excipient are studied; if no degradation is observed then the compounds are assumed to be compatible and no further assessment is necessary. If an incompatibility is observed, the system is abandoned or further experiments carried out to identify the cause.

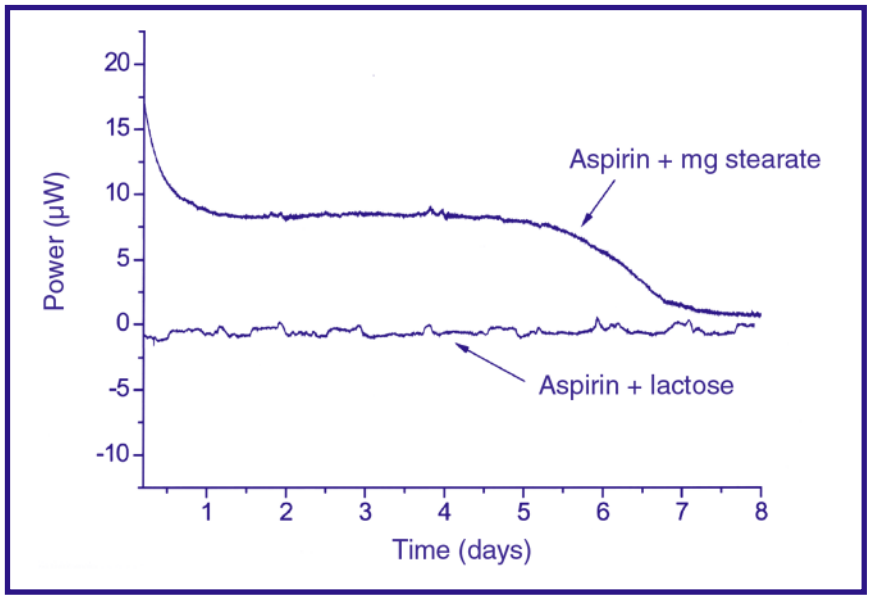

Figure 1. Power-time data for binary mixtures of aspirin/lactose and aspirin/magnesium stearate, both under an RH of 100% [Reproduced with permission][19]

DSC is widely used for compatibility screening.[6-11] The basic methodology used is simple; the thermal responses for the API and excipient(s) alone are compared with those recorded for the API blended with a range of excipients. Any changes in the expected peaks, or the appearance of new thermal events, indicates a likely incompatibility. The major benefit of using DSC for primary screening is one of time; an initial judgement on likely incompatibilities can be made in a few minutes. However, the same caveat applies to the interpretation of DSC stability data as for all elevated temperature stability assessments; it must be assumed that the reaction mechanism doesn't change as a function of temperature.

If an accelerated stress test is required then the thermal behaviour under a controlled relative humidity (for example, 75%) of the active alone and the excipient alone can be recorded and compared with that determined for a binary mixture. Note that these initial screens are usually designed to maximise the chance of seeing an interaction, if there is one, rather than match the conditions of the intended formulation; thus, binary samples are usually mixed in a 1:1 ratio, ensuring the two materials have equivalent particle sizes, and a high RH is used. Further screens under more representative conditions can then be conducted if required.

The well documented incompatibility between aspirin and magnesium stearate[18] provides an ideal system to demonstrate the use of IC to investigate API-excipient mixtures. Under an RH of 100%, a binary mixture of aspirin and lactose shows no thermal response while a binary mixture of aspirin and magnesium stearate shows a large exothermic signal, **Figure 1**. Analysis of the aspirin content in the ampoule after the power had returned to zero showed that the entire drug sample had degraded.

Interactions between a solid active and a range of excipients, including potato starch, α-lactose-monohydrate, micro-crystalline cellulose (MCC) and talc have been investigated using IC, albeit between elevated temperatures of 60-80°C.[20] Large exothermic heat responses

were observed for mixtures of drug with MCC, potato starch and lactose, indicating these systems were unstable.

Flow micro-calorimetry has been used to study the interaction between heparin sodium and dopamine hydrochloride in two parenteral formulations.[22] A significant interaction between the drugs was noted when dextrose was included in the parenteral solution which was not seen in normal saline formulations.

Stability

The approach adopted in the above studies does not quantify the amount of degradation nor does it indicate the nature of any degradation processes. It does, however, allow an initial judgment to be made on the likely stability of a compound or mixture, giving the formulator valuable insight into the stability of the API to be formulated or which excipients are likely to result in a stable product. As such, the use of IC during initial product formulation offers the potential greatly to reduce the number of potential formulations undergoing stability essays. IC data can also aid in the continuing development of existing products, whose stability has been assessed and accepted using classical methods. In this case, the thermal response from the API with new excipients and/or packaging materials can be recorded; the lack of a detectable heat signal provides good evidence that no new incompatibility reactions will be introduced into the new product and that the existing stability data are still applicable.

Although IC offers considerable benefits in determining product stability, ultimately it will never replace the need for chemical analysis; this area forms a considerable challenge that must be overcome if IC is to become more widely used for pharmaceutical stability assessment.

Development of drug delivery systems

The benefits of using IC for compatibility assessment are clear but the benefits for formulated products are perhaps even greater. This is because of the stability of the technique to monitor the sample over time. The only issue facing the operator is to select a fraction of the sample for investigation that is representative of the whole.

IC can also be useful in the development of drug delivery systems; for example, investigating the swelling of polymers often used in modified release systems. Conti *et al* noted that the observed rate of drug release from a polymeric drug delivery system is governed by a combination of diffusion, swelling and erosion so it is not a simple task to determine the effects of the polymer on the observed drug release rate. They dispersed powdered polymer samples in water or buffer in a calorimeter and the heat associated with the swelling phenomena was recorded.

Dissolution occurred immediately following hydration of the polymer. Properties of the polymer blends were different from those of either constituent and correlated with those seen for polymer tablets during dissolution experiments. The data implied that solution calorimetry could be used to construct quantitative structure-activity relationships (QSARs) and hence to optimise selection of polymer blends for specific applications.

Summary

Calorimetric techniques offer a number of unique benefits for analysis of pharmaceuticals. They are thus ideally suited to many areas of pharmaceutical development. However, data interpretation is not necessarily straightforward and can be dependent upon sample preparation as well as the type of instrument used.

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SODIUM CONTENT OF EFFERVESCENT ANALGESICS

by Ingo Friedrich, Alfred Bonatz and Karla Schwenke

Introduction

It is generally recommended that a reduction of salt intake by the population would be of benefit thereby reducing the incidence of cardiovascular disease.

Whilst dietary salt intake accounts for most of the population's salt intake, it would appear sensible not to increase one's salt intake unnecessarily. Thus, any medication that needs to be taken, whether on prescription or self-prescribed, should have the least possible sodium content, all other factors being equal.

As effervescent formulations need to include significant amounts of sodium in the form of sodium bicarbonate it was thought useful to make a comparison of effervescent formulations of several common analgesics.

Materials and methods

Effervescent tablets of widely available brands of paracetamol, and paracetamol combined with either codeine or tramadol, were purchased from community pharmacies in Europe (**Table**).

Two tablets of each were analysed to determine their sodium content. The tests were carried out by Currenta GmbH & Co. OHG, Leverkusen, Germany using ICP-OES (Inductively Coupled Plasma Optical Emission Spectrometry), a technique widely used to determine concentrations of a wide range of elements in solution, especially the lighter elements in the periodic table, principally the alkali metals.

Tests were performed in duplicate.

Results

Figure 1 shows the sodium content of each of the effervescent products. It is clear that there is a wide variation between the products, with the paracetamol/tramadol product (Zaldiar® Effervescent) containing less than half the sodium of four of the products and less than one third of the two other products.

The products containing only paracetamol as the active ingredient, contained the highest amount of sodium.

Discussion

Whereas the paracetamol/tramadol effervescent tablet contains the commonly used excipients to produce effervescence, ie. citric acid, sodium citrate and sodium bicarbonate, it was evident that it contains fewer of these excipients than the other brands tested, resulting in having less than half their sodium content. Whilst not included in the study, it is interesting to note that each tablet of the widely used analgesic brand, Alka-Seltzer, contains 551mg sodium which would put it among the higher sodium-containing products.

From the patient's point of view, effervescent tablets have a number of advantages over solid tablets and capsules and liquids: they have a faster absorption and onset of action, the medicament being in a solution or dispersant; there is no need to swallow tablets – an important consideration for elderly patients. Moreover, they can incorporate relatively large amounts of active ingredients per unit dose.

The Recommended National Intake (RNI) of sodium for healthy adults in the UK is 1,600mg. In the USA the Daily Reference Value (DRV) of sodium is 2,300mg, although the American Heart Association recommends not more than 1,500mg sodium/day. Thus, as the usual dose of the analgesic products tested is 3 to 4 tablets a day, patients would exceed or come near to exceeding the recommended limits of sodium intake by taking any of the tablets tested, with the exception of the paracetamol/tramadol combination.

Clinical considerations

Most of the clinical studies assessing the effect of a modest reduction of salt intake on blood pressure show a small but significant reduction in blood pressure in patients with hypertension. There is also solid evidence that even a small

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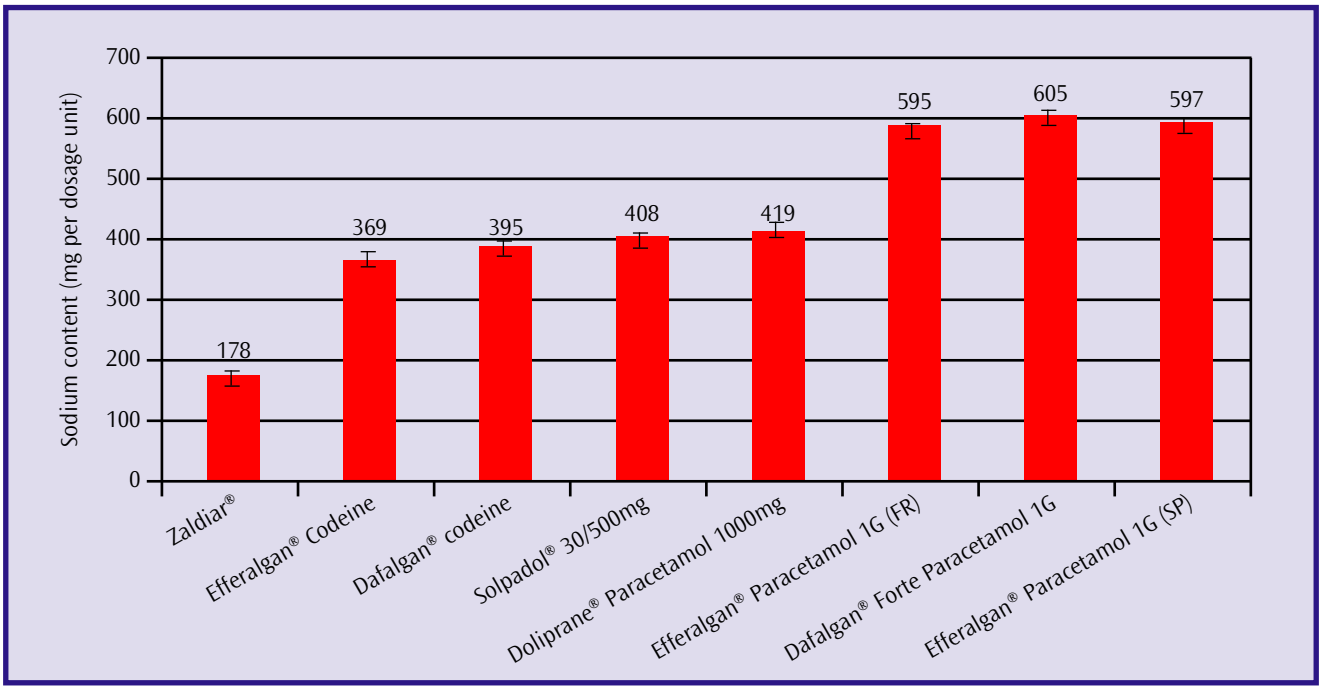

Figure 1. Sodium content per dosage unit of effervescent tablets (n=2). FR = France, SP = Spain

Table. Overview of investigated drug products. FR = France; SP = Spain

Drug Product	Active ingredients	Marketing authorization holder
Zaldiar® effervescent tablets	Paracetamol 325mg Tramadol 37.5mg	Grünenthal
Efferalgan® Codeine effervescent tablets	Paracetamol 500mg Codeine 30mg	BMS
Dafalgan® Codeine effervescent tablets	Paracetamol 500mg Codeine 30mg	BMS
Solpadol® 30/500mg effervescent tablets	Paracetamol 500mg Codeine 30mg	Sanofi Aventis
Doliprane® Paracetamol 1000mg effervescent tablets	Paracetamol 1000mg	Sanofi Aventis
Efferalgan® Paracetamol 1G effervescent tablets	Paracetamol 1000mg	BMS
Dafalgan® Forte Paracetamol 1G effervescent tablets (FR)	Paracetamol 1000mg	GMS
Efferalgan® Paracetamol 1G effervescent tablets (SP)	Paracetamol 1000mg	BMS

reduction in blood pressure can reduce the incidence of cardiovascular events such as coronary heart disease, stroke and myocardial infarction.

It is generally recommended in the US (National Institute of Health), UK (Food Standards Agency) and Europe (European Society of Cardiology) from a public health point of view that there should be a reduction in the daily intake of salt by the general population, especially those at risk.

On the other hand, neither the safety nor the benefit of long-term reduced sodium intake in hypertensive patients has been established in epidemiological studies.

Conclusions

Whilst the benefits of reducing sodium intake in normotensive or hypertensive patients is unclear, it would be sensible to reduce dietary salt and choose a medicament with the lowest sodium content of comparable products.

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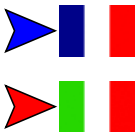
DATAMATRIX ADOPTED BY FRENCH PHARMACEUTICAL INDUSTRY

By Frédéric Lemaire

As of 1st January 2011, new regulations created by the AFSSAPS (French Agency of Sanitary Safety and Health Products) will establish an improved coding standard for the French pharmaceutical market. The new standard is designed to improve the traceability of medicines distributed in France and to increase consumer safety. From now on, a Datamatrix barcode containing the new CIP-13 code, a batch number and the medicine expiry date will be printed on the production line as a replacement for the current French pre-printed CIP-7 standard.



As a result, the quality of traceability will move to a higher level. The Datamatrix code will contain a unique number printed on each pack, in accordance with the new principle of 'serialisation'

Improving the distribution of pharmaceutical products

This regulation derives from the need to increase the control of the supply chain of medicines in order to guarantee the safety of patients. The traceability of medicines is a crucial issue for hospitals and healthcare establishments. According to surveys, in Europe around 1% of prescriptions is improperly dispensed, which represents one to two million medical incidents per year for a country such as France.

The aim of the new standardisation is to improve the efficiency of batch recalls, to reduce errors, to combat counterfeiting and reimbursement fraud and to increase the transparency of the distribution chain. From 2011 onwards, manufacturers, distributors, pharmacies and hospitals will be required to trace products by an electronic receipt notice (EDI).

The new regulation will enable pharmaceutical companies to know quickly and accurately what they have supplied, both to the distributors and to the hospitals, but traceability often stops there.

The strong point of this new regulation for the supplier is that it will send the information included in the Datamatrix code electronically. It will allow automatic integration by the various players in the traceability information chain, while also improving product monitoring and enhance flow management. In a nutshell, the regulation improves the traceability of products from the production chain to the patient's bed.

Possible European standardisation

France and Turkey are the first two countries to adopt the Datamatrix system in their traceability regulations. What has become an official regulation in France could be shared by all of Europe in the future, given that EFPIA (European Federation of Pharmaceuticals Industries and Associations) recommends the adoption of the Datamatrix system to GS1 standards as a common traceability standard. In fact, Germany, Spain and Italy envisage adopting the Datamatrix system in the future.

Advantages of the Datamatrix system

The Datamatrix marking system was chosen due to the need to encode more information on each label but maintaining a print size small enough to allow use on pharmaceutical packaging. Datamatrix marking allows a large storage capacity (more than 3,000 characters) on minimal physical dimensions, thanks to 2D coding. The additional information contained in the code facilitates the electronic automation of product monitoring in the supply chain to allow batch recalls or automatic detection of out-of-date products. Finally, its cost remains very competitive (marking cost between 0.1 to 0.2 eurocents per pack).

Pharmaceutical companies must adapt their supply chains

Pharmaceutical manufacturers will be obliged to install new printing systems for

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Avery Dennison is an international consultancy company offering innovative and flexible solutions for Datamatrix marking and control, and is one of the first suppliers to propose complete Datamatrix integration solutions.

With a Datamatrix code, the information is encoded very compactly in a square or rectangular area as a pattern of dots.

the Datamatrix marking in order to satisfy the new regulation criteria.

Thus French and international manufacturers who wish to distribute medicines on the French market will have to buy appropriate equipment in order to comply with this new regulation. The difficulty of implementing this new marking lies in the correct integration of the new printing and control system.

The main constraints for pharmaceutical managers are the lack of space on production lines for adding new labelling equipment, the multiplication of interfaces and communication issues between the different elements (marking, control, automation, line supervision, etc.) as well as the need to ensure product packs are delivered to the label applicator consistently and accurately.
First, existing labelling machines need to be upgraded without affecting the dimensions. The update of the AVL labeller is a cost-effective upgrade of a proven labelling machine, but with new features added.

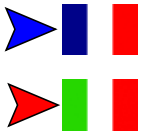
Second, the production line needs to be updated to ensure accurate and consistent movement of product packs through the labelling area provides the best print quality. Establishing an effective medicine traceability system is a major challenge for pharmaceutical companies. France is the first country to standardise the use of Datamatrix code, but it is a regulation that will ultimately become the standard worldwide. Companies are generally aware of the challenges presented. They will need the right equipment but will also need the aid of experienced contractors to provide them with reliable and easy to integrate solutions.

CHLORHEXIDINE: SKIN PERMEATION AND ANTISEPSIS

by Tarja J Karpanen, Emma R Hendry, Tony Worthington, Peter A Lambert and Barbara R Conway

Introduction

The skin is an intricate habitat for a diverse population of microbiota comprising both transient and commensal skin micro-organisms. It is composed of a variety of niches such as hair follicles, sebaceous, eccrine, and apocrine glands, forming sub-habitats with a broad range of pH, temperature, moisture, and sebum content that may be associated with their own unique microbiota. Resident micro-organisms such as Staphylococcus spp., and other Gram-positive bacteria, are able to survive and proliferate and may have beneficial roles including inhibition of pathogenic species and further processing of skin proteins, free fatty acids and sebum.



Molecular detection techniques have found evidence for 182 different species of bacteria in skin samples, 8% of which were unidentified[1]. Furthermore there is considerable variation in microbial diversity between individuals and at different skin sites on the body[2]. Many antimicrobial agents exhibit restricted permeation of the skin and fail to reach the deeper layers, including the hair follicles and persisting micro-organisms in the lower areas of the skin may be able to cause infection when the protective skin barrier is breached during surgical procedures.

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Healthcare associated infections and antisepsis procedures

It is estimated that 8.2% of hospital patients in England in 2006[3] acquired infection whilst in hospital, a figure that is influenced by health of the patient, immunosuppressive therapies and the invasive nature of the procedure. Surgical site infections (10.7%) and blood stream infections (6.2%)[4] are often associated with resident or transient skin micro-organisms could be reduced by adequate hygiene measures including appropriate asepsis during invasive procedures. Elimination of micro-organisms in the lower layers of skin may in turn reduce microbial contamination of the incision site by the deep seated micro-organisms during an invasive procedure. In addition, it may also reduce the likelihood of re-seeding of micro-organisms onto the skin surface following skin antisepsis, therefore again reducing the risk of infection. Effective and rapid permeation of the applied antiseptic agent into deeper layers of the skin is essential in preventing infections associated with invasive procedures.

The most commonly used antiseptics for skin preparation prior to invasive procedures are alcohols, chlorhexidine gluconate (CHG) and povidone-iodine (PVP-I), of which CHG and PVP-I have shown more persistent antimicrobial activity compared to alcohols alone. Current guidelines for skin antisepsis prior to insertion of intravascular catheters, such as central venous catheters (CVC), recommend 2% (w/v) CHG, preferably in 70% (v/v) isopropyl alcohol (IPA)[4].

CHG is a biguanide antiseptic with a broad spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria, yeasts and some lipid-enveloped viruses, but has little effect on mycobacteria, spores and most viruses. It has been shown to bind to the stratum corneum (SC) intercellular cholesterol with high affinity, without removing the endogenous cholesterol, and accumulate in the SC layer without penetrating through the SC due to its large molecule size[5].

Penetration enhancers

Developments in the transdermal delivery of drugs offer a potential solution to improvement in the penetration of antiseptic agents into the skin. Penetration enhancers can improve solubility of the drug in the stratum corneum and facilitate diffusion through the barrier layer by disrupting the packing of skin lipids and thus altering the barrier nature of the stratum corneum. Additionally, they can influence

the partitioning behaviour of the drug at the stratum corneum-viable epidermis interface and affect the thermodynamic activity of the drug.

Terpenes bind in large quantities to SC and act as skin penetration enhancers by increasing drug partitioning into the skin (solvent effect), as well as enhancing drug diffusion and reversibly disrupting lipid bilayers[6].The lipid disruption is reversible and 1,8-cineole does not result in lipid depletion from the SC[7]. Furthermore, these volatile compounds may alter the thermodynamic activity of the drug due to evaporation of terpenes post application. Eucalyptus oil, comprising the main constituent 1,8-cineole, may therefore serve as a suitable candidate for enhancing the delivery of CHG into the skin, including hair follicles and sebaceous glands, where many micro-organisms reside.

Synergistic antimicrobial activity

We have shown that the combination of EO and CHG exhibits synergistic antimicrobial activity against bacteria in suspension and biofilm modes of growth[8]. The synergy between the crude oil and CHG is better than the single terpene, 1,8 cineole against a range of clinically relevant micro-organsims[9] (**Tables 1** and **2**). It is likely that the synergy observed may

Table 1. Antimicrobial activities of EO, 1,8-cineole and aqueous CHG against *S. aureus, MRSA, P. aeruginosa, E. coli* and *C. albicans* growing in suspension.

Micro-organism	Combination Tested	MIC of oil (g/L) alone/in combination		FIC of oil (average)	MIC of CHG (mg/L) alone/in combination		FIC of CHG (average)	FICI (average)	Result
S. aureus	EO + CHG	32/8	32/4	0.188	1/0.125	1/0.125	0.125	0.313	Synergy
	Cineole + CHG	128/4	128/4	0.031	1/0.25	1/0.25	0.250	0.281	Synergy
MRSA	EO + CHG	16/4	16/4	0.250	2/0.25	2/0.25	0.125	0.375	Synergy
	Cineole + CHG	128/8	128/4	0.047	0.5/0.125	0.5/0.125	0.250	0.297	Synergy
P. aeruginosa	EO + CHG	16/4	16/8	0.375	4/2	4/1	0.375	0.750	Indifference
	Cineole + CHG	256/4	256/4	0.016	4/2	4/2	0.500	0.516	Indifference
E. coli	EO + CHG	8/1	8/1	0.125	0.5/0.25	0.5/0.125	0.375	0.500	Synergy
	Cineole + CHG	32/8	32/8	0.250	0.5/0.125	0.5/0.125	0.250	0.500	Synergy
C. albicans	EO + CHG	8/2	8/2	0.250	4/1	4/1	0.250	0.500	Synergy
	Cineole + CHG	32/4	64/4	0.094	2/0.5	2/1	0.375	0.469	Synergy

EO, eucalyptus oil; cineole, 1,8-cineole; CHG, chlorhexidine digluconate.

Table 2. Antimicrobial activities of EO and aqueous CHG against *S. aureus, MRSA, P. aeruginosa, E. coli* and *C. albicans* growing in biofilm.

Micro-organism	Combination Tested	MIC of oil (g/L) alone/in combination		FIC of oil (average)	MIC of CHG (mg/L) alone/in combination		FIC of CHG (average)	FICI (average)	Result
S. aureus	EO + CHG	128/4	128/4	0.031	16/4	16/4	0.250	0.281	Synergy
	Cineole + CHG	256/32	256/32	0.125	16/8	16/8	0.500	0.625	Synergy
MRSA	EO + CHG	256/4	256/4	0.016	8/1	8/1	0.125	0.141	Synergy
	Cineole + CHG	128/4	128/4	0.031	16/4	16/4	0.250	0.281	Synergy
P. aeruginosa	EO + CHG	>256/32	>256/32	0.125	64/16	64/16	0.250	0.375	Synergy
	Cineole + CHG	>256/4	>256/4	0.016	16/4	16/4	0.250	0.266	Synergy
E. coli	EO + CHG	16/4	16/4	0.250	16/8	16/8	0.500	0.750	Indifference
	Cineole + CHG	64/4	64/4	0.063	16/0.5	16/0.5	0.031	0.094	Synergy
C. albicans	EO + CHG	64/4	64/4	0.063	16/0.5	16/0.5	0.031	0.094	Synergy
	Cineole + CHG	16/16	16/16	1.000	16/2	16/2	0.125	1.125	Indifference

EO, eucalyptus oil; cineole, 1,8-cineole; CHG, chlorhexidine digluconate.

result from activity against the target cytoplasmic membrane resulting in damaging the structural stability of the cell and increased permeability.

Skin permeation

Aqueous chlorhexidine demonstrated poor permeation into the deeper layers of the skin, which may restrict the efficacy of skin antisepsis with this agent[10]. There was no detectable penetration through full thickness human skin in an *in vitro* model designed to study the depth of penetration of agents into the skin. The outer layers of the skin, (SC and other epidermal layers) contained the highest amount of CHG following exposure to the antiseptic solutions from 2 minutes up to 24 hours. Whilst chlorhexidine in alcoholic solution has clearly been shown to have superior antimicrobial activity compared to aqueous CHG, efficacy in reducing catheter colonization and infection is comparable[11, 12]. Alcohol, at a concentration of 70% (v/v) has rapid antimicrobial activity against a broad spectrum of micro-organisms but has also been shown to extract important lipid components of the SC and to cause dehydration of SC proteins, thus potentially compromising the permeation of CHG within the skin[13]. We have shown that CHG permeation into the deeper layers of skin was significantly improved with EO compared to CHG in aqueous solutions or in 70% (v/v) IPA[14]. Furthermore, 2% (w/v) CHG in combination with 70% (v/v) IPA and 10% (v/v) EO significantly increased the amount of CHG penetrating into the skin within 2 minutes compared with CHG/IPA (**Figure 1**).

Summary

Micro-organisms colonising the skin reside not only on the external surfaces but are also found to inhabit hair follicles and sites beneath the skin surface. They can cause infection when the protective skin barrier is breached. Effective skin antisepsis is therefore required for preventing infections associated with invasive procedures and an efficient and rapid permeation of the applied antiseptic agent into the deeper layers of the skin is essential in skin preparation prior to invasive procedures.

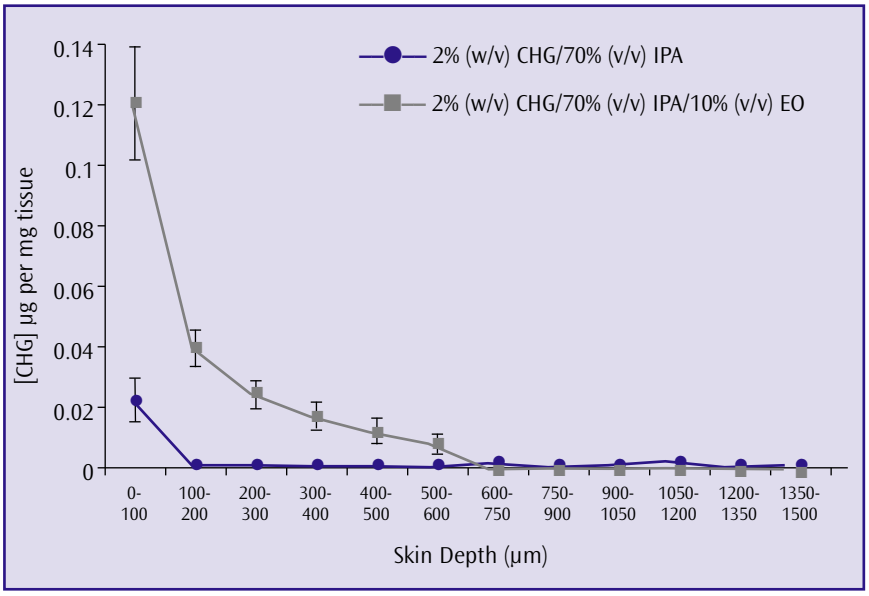

Figure. Penetration profile of CHG into full thickness human skin following exposure for thirty minutes with CHG in alcohol (70% v/v IPA) (n=15; mean ± SEM) and CHG in 70 % v/v IPA with 10%v/v EO (n=10; mean ± SEM)

Chlorhexidine is one of the most widely used antimicrobials within clinical practice for skin antisepsis and is used in both aqueous and alcoholic solutions. We have demonstrated the limited permeation of CHG into a human skin model following application of either alcoholic or aqueous solutions. Moreover, the negligible concentrations of chlorhexidine detected at sites deep within the tissue may indeed allow for micro-organisms residing in the deeper layers, for example around hair follicles, to survive the skin antisepsis procedures recommended in the current guidelines.

In the light of increased antimicrobial resistance within the clinical setting, the potential of essential oils for the prevention and treatment of infection has been researched in several studies. We have demonstrated a synergistic antimicrobial activity of chlorhexidine and essential oils including eucalyptus oil and have shown that the combination of eucalyptus oil and chlorhexidine applied at the skin surface increases both the rate and extent of delivery of chlorhexidine within the deeper skin layers. Such a combination may aid in preventing infection and microbial re-colonisation of the skin in clinical practice following invasive procedures.

Conclusion and perspectives

The delivery of effective antiseptics into the lower layers of the skin may be an useful strategy for improving skin antisepsis. Our results lay the foundation for further research within the field of skin antisepsis with a view to developing improved formulation strategies for use of CHG in clinical practice. Both skin penetration and antimicrobial efficacy of CHG can be enhanced by combination with EO, which in turn may improve

access to further micro-organisms present in the skin, thereby enhancing antisepsis. Results from these studies highlight the opportunities available to adopt alternative strategies that may enhance the effectiveness of skin antisepsis in clinical practice.

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REGULATORY REVIEW

Review of major developments in GMP in the EU and USA, September to December 2010

by Malcolm Holmes

Introduction

The current review period has seen a number of changes in the regulation and regulatory guidance.

The most significant of these relate to proposed changes in the EU GMP Chapters 5 & 7, CEP suspensions by EDQM, progress on Joint inspections by FDA /EMEA and the requirement for responsible Person Assessment in the UK.

Europe

EC

Public consultation – revised chapters 5 & 7 of the EU GMP
The changes proposed in chapter 5 relate to the qualification of suppliers of starting material, supply chain traceability for starting materials and the testing of starting materials.

The revision of Chapter 7 takes into account ICH Q10 and provides guidance on outsourced activities beyond the current scope of contract manufacture and analysis operations.

EDQM

Certification of Suitability to the Monographs of the European Pharmacopoeia (CEP) Suspensions
EDQM has updated its listing of suspension of CEPs. 8 CEPs were suspended as a result of inspection of manufacturing sites. 3 more were suspended for failure to comply with a declaration of willingness to be inspected and/or to operate according to EU GMP. A further 5 were suspended due to a failure to fulfil, after a suspension, the requirements of the CEP procedure with regards to updating the application and complying with GMP. Impacts from such suspensions on companies which have sourced the affected API may well affect the ability to maintain supply of new product. Companies may need to consider any necessary actions in relation product currently on the market.

EMA

EMA/FDA joint GMP inspection pilot programme-Terms of reference and procedures
EMA/FDA have published a paper to outline the proposal for joint inspections between FDA/Center for Drug Evaluation and Research (CDER) and EU National Regulatory Authorities.

Companies requiring either pre- or post-approval inspections may contact the FDA/CDER and/or EMA to express interest in a joint inspection.

CHMP

Confirmation that presence of unexpected viral DNA in live attenuated vaccines does not raise public health concerns
A CHMP Expert Committee has concluded that the presence of unexpected viral DNA in such vaccines does not pose a risk to public health, because the type of virus found does not cause disease in humans.

Following the detection of viral fragments in manufactured vaccines researchers tested different vaccines using metagenomics methodology. When this method was applied to vaccines, the researchers found unexpected viral DNA from porcine circovirus (PCV, a virus commonly found in meat and other foods) in rotavirus vaccines.

Porcine trypsin, a reagent used in the vaccine production process, was the most likely cause for the presence of PCV.

Metagenomic testing could be used as an additional tool to the current standard testing methods for vaccines. However, given its novelty and the absence of standardisation, it cannot yet be requested as a standard for testing and control.

CHMP, US FDA, WHO & EDQM, are discussing a common approach for the use of Metagenomic testing in biological medicines.

MHRA

Review of GMP deficiency data from April 2008 – March 2010 and GDP deficiency data from July 2009 to June 2010
New GMP and GDP deficiency data review information has been added to the GMP and GDP sections of the MHRA website. The top five deficiencies over a two year period are indicated. The GMP section includes examples of actual deficiencies found and the GDP section shows deficiency trends.

Updated risk-based GMP & GDP inspection statistics from
For GMP inspections 30% of sites will receive reduced inspection frequency. The impact will be less inspection time on site per annum. No sites have yet been allocated category V, which would give them an inspection frequency of 30 months with up to 50% reduction in time on site. None of the 421 sites inspected were scheduled for immediate re-inspection, but 9 were scheduled for re-inspection within 6 months.

For GDP inspections, 602 inspections were conducted on WL holders. 60.8% were conducted at the maximum 4 year inspection

frequency and 4% at the minimum 6 month frequency.

Third country voluntary investigational medicinal products (IMP) inspections
The MHRA GMP Inspectorate is no longer able to carry out voluntary IMP inspections in third countries. This may cause some problems for companies which have previously been inspected where current GMP Certificates are expiring.

Consolidation and review of UK medicines legislation
Publication of a second informal consultation on opportunities identified to reduce regulatory burdens as part of the project to consolidate and review UK medicines legislation.

MHRA Provision of Responsible Person (RP) training and assessment
MHRA plans to introduce minimum qualifications for the Responsible Person.

Companies, organisations or individuals interested in becoming involved in the provision of RP training and assessment were invited to a meeting at the MHRA office in York on 17 December 2010 to discuss proposals.

New and existing RP's will need to possess a statement of eligibility to be named on a wholesale dealer licence. There will be a two year transition period for existing RPs to gain eligibility.

International

PIC/S

Two new Participating Authorities
The US Food and Drug Administration and Ukraine's State Inspectorate for Quality Control of medicines were invited to Join PIC/S as from 1 January 2011.

FDA is PIC/S' 38th Participating Authority and SIQCM the 39th.

WHO

Guideline on quality Risk Management
This new guideline, was presented/ discussed at the 45th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The document is of interest to both industry and regulators world-wide. Whilst consistent with ICH Q9 it contains in addition some interesting processes such as a "checklist for inspecting QRM" and a "process for the inspection of risk based decisions".

The guideline adds a further two primary principles of QRM which emphasise the dynamic aspects of and the need for continual improvement of QRM

A monthly Regulatory Review is available to subscribers to "GMP News" published by Euromed Communications. (www.euromedcommunications.com)

NEWS FROM THE EIPG

Strategic plans for EIPG

A teleconference between eight delegations to discuss the future activities of EIPG was held last November and proposals were taken forward during a Strategy meeting in Paris on 29th January. This was informed by the responses from individual members to the questionnaire on "What do we want from EIPG?" A large number of ideas and comments are being prioritized and will be discussed with delegations during the General Assembly in Madrid.

One of the areas of concern is the lack of adequate two-way communication between individual members and the Bureau. The EIPG Journal offers a "letters page" and the website has discussion facilities. Either way, we would like to hear your opinions and to learn about your activities in Industrial Pharmacy.

Student contact

In December, Pär Tellner, Vice-President Education and Careers from Sweden and Kristina Bindus, Vice President European Affairs from Belgium had a meeting with Sanziana Marcu-Lapadat, EPSA Vice-President of External Affairs.

It was agreed that EPSA will advertise careers in the pharmaceutical industry via circulars and on their website. Anyone wishing to add a national viewpoint on careers in industry should write in the first instance to Sanziana at *vp.ea@epsa-online.org*. The EPSA General Assembly will be held in Lisbon, 11-16 April 2011 with the theme of pharmaco-vigilance.

Through our Journal and website, EIPG agreed to advertise the EPSA Individual Mobility Project which aims to provide pharmacy students and recent graduates with work or research experience in another European country.

European Commission

EIPG was invited by the European Commission to a meeting on curriculum design and development from the perspective of University-Business cooperation. Representing the close collaboration between the pharmaceutical industry and academic pharmacy were Antje Marquardsen, President of our member association Pharma-danmark from an industrial perspective and Professor Bjarne Fjalland past- Vice-Dean of the Faculty of Pharmaceutical Sciences at the University of Copenhagen from an academic perspective. The findings of the seminar will feed into the discussions of the next University-Business Forum that will take place in Brussels on 22-23 March 2011. Anyone interested in reading a copy of the minutes, please contact me.

The Professional Qualifications Directive (2005/36/EC) is out for consultation and we have until mid-March to comment. Anyone wishing to contribute to updating the Directive please contact me.

European medicines agency

The 59th GMP/GCP working group meeting with interested parties was attended by our President, Gino Martini and John Jolley, GB delegate. John's report of the meeting is published as follows, and summarises the numerous GMP initiatives under consideration by the regulators.

Jane Nicholson, Executive Director EIPG, jane@nicholj.plus.com

59th Meeting of GMP/GCP Working Group

The meeting at the EMA was chaired by David Cockburn and considered the following:

Update on work plan of GMP/GDP IWG – EMA

The following revisions are to be made to the EU GMP Guide:

Part III

GMP Guide is to include a New Part III intended to host a collection of GMP related documents, which are not interpretive guidelines on the principles of GMP laid down in Directives 2003/94/EC and 91/412/EC.

Chapters 1 & 2

Updated in line with concepts and terminology of ICH Q10

Consultation ended May 2010

Chapters 3 & 5 (dedicated facilities)

Revised strategy agreed, work in progress

Other changes to Chapter 5

Qualification/verification of API supply chain

Testing of starting materials

Chapter 6

Revision needed to reflect current practice in analytical method transfer

Concept paper under development

Chapter 7

Revision to reflect modern practices in outsourcing

Work in progress

Chapter 8

Introduction of reporting responsibilities in case of product

shortages due to manufacturing problems.

Concept paper under development

The following revisions are to be made to the annexes to the GMP Guide:

Annex 2 (Biological)

2nd public consultation ended 15 July 2010

Annex 11 and consequential changes to Chapter 4

Final agreement expected by GMP/GDP IWG before the end of 2010

Annex 14 (Blood Products)

Agreed by GMP/GDP IWG March 2010

– Undergoing review by EC's Legal services.

Annex 15 (Validation)

– Awaiting QWP guideline on process validation

Annex 17 (Parametric Release)

awaiting QWP guideline on Real Time Release Testing

GDP

EU GDP guide under revision

The Work Plan of the GMP/GCP IWG for 2011 will include:

• New module of the EUDRA GMP is to be developed for 3rd country inspection planning subject to budgetary approval

Implementation of "anti-falsification legislation" – EMA/EGA

A range of documents are expected to require development in order to implement the future anti-falsification legislation. No comments were made by the meeting

Opportunities for industry involvement in guideline development – EFPIA

EFPIA did not present a paper, but repeated their request for consultation in the preparation of new EMA guidelines.

Proposal to revise GMP Annex 16 for "minor deviations" – IFAH-EU

IFAH-Europe would welcome a revision of Annex 16 to the GMP guide and asked that it include the concept described in the Reflection Paper on 'minor deviations'. This revision could be part of the GMP/GDP Inspectors Working Group work plan for 2011.

Currently, Annex 16 prevents a QP from releasing a batch that deviates from its marketing authorisation – see section 2.2 of the Annex that reads: *"The purpose of controlling batch release in this way is:*

• *To ensure that the batch has been manufactured and checked in accordance with the requirements of its marketing authorisation,"*

To provide for situations where such release could be allowed, the GMP/GDP Inspectors Working Group published in March 2006 a Reflection Paper. At the time, the possibility to amend Annex 16 accordingly was also given in the document (see last § of the March 2006 draft version that reads: *"This interpretation of the requirements is published here in the form of a reflection paper and comments are invited. The European Commission is ready to support the principles being implemented as an amendment to Annex 16 of the GMP Guide depending on feedback on practical aspects.")*. The Reflection Paper was slightly revised in 2008 and made publically available.

In order to fully implement the concept, IFAH-Europe recommends it is now introduced in Annex 16. This will provide the QP with a binding text to justify its decision for releasing a batch with 'minor deviations'. Furthermore, it will ensure a consistent approach by all competent authorities regarding QP discretion in such cases.

EIPG requested that Annex 16 be revised as the current version had not been updated in the last 15 years and that the many inconsistencies with current practice led to confusion.

EMA noted the request and said that changes to the guideline would be considered, but limited resources would restrict them from rewriting annex 16.

Site Master File and role of QP – IFAH-EU /QPA

Feedback to the comments submitted during the public consultation on a new Proposed GMP new Part III on Site Master File requested that:

• SMF must have no statutory force, as stated on the cover page of the draft proposal.

• Electronic format (e-mail) to be accepted by all competent authorities.

• Submission, approval and maintenance: all to be carried out electronically and facilitated.

• According to the EU GMP Part III "Explanatory notes…"
This "informational Part III of the EU GMP Guide is created for documents which are not themselves GMP guidelines and have no statutory force but which complement the GMP guideline".

• Please confirm that there are no intentions to make a Site Master File mandatory on a European level.

• Please specify if there are any expectations to a certain role of the QP in that respect (Site Master File or Quality Manual)

IFAH-Europe said that they would welcome some feedback to the comments submitted during the public consultation on a new GMP

Part III that closed in March; they especially wish to gain confirmation that the SMF will have no statutory force, as stated on the cover page of the draft proposal.

Furthermore, IFAH-Europe would welcomed the agreement by all competent authorities to accept receiving such document electronically, i.e. in pdf or Word format sent by e-mail.

Role of QP in supply chain oversight – QPA

The QP Association questioned whether the QP personal responsibilities should include responsibility for all stages of the supply chain. However the resultant discussion agreed that the QP should take responsibility, but EIPG stated that the regulations did not restrict the QP from delegating the audit process even though they may value the responsibility.

Dedicated facilities (APIs) – CEFIC

CEFIC welcomed the EMA Update on revision of Chapters 3 and 5 of the GMP Guide on Dedicated Facilities as APIC fully recognizes industry's responsibility to ensure there is No Risk of Harm to Patients caused by ineffective controls during the manufacturing, packaging and handling of APIs, and support strong focus during Regulatory/GMP Inspections on the effectiveness of the Controls and Procedures in place for any High Risk operations regarding:

- Effective controls for dedicated facilities
- Cleaning procedures for equipment and facilities
- Cleaning validation of multi-product equipment
- Good Hygienic Practices of operators in contact with products

They request that their comments on API/intermediates are also addressed.

It was also noted that:

- FDA are also currently working on a similar guidance on dedicated facilities
- APIC, ISPE and others are offering guidance on cleaning validation
- In the interest of safety of patients worldwide, cooperation and interaction between industry and the regulators would be the best way forward
- Therefore, APIC suggests that "dedicated facilities/cleaning validation for multi-purpose equipment" should be adopted as an ICH Topic

Risk-based auditing – PDA

In the paper presented by PDA they proposed a Paradigm Change in Manufacturing Operations' (PCMO) that would achieve the following:

- Dialogue with regulators focusing on manufacturing needs
- Provide scientific expertise according to new paradigm
- Give examples on "How-to-do"
- Proposed manufacturing topics not covered so far by other organisations
- Establishing best practice documents/training to assist industry in implementing the ICH Q8, Q9, Q10 & Q11 guidelines
- This project facilitates communication among the experts from industry, university and regulators as well as experts from the respective ICH Expert Working Groups and Implementation Working Group to be reflected in EU GMP guide.

EU-wide acceptance of risk-based justification of derogation to the requirements to use GMP compliant APIs for atypical actives to continue.

NCAs to signal endorsement of risk-assessment approach recommended in the EMA Q&A on their website, as part of national implementation of EU GMP guide. At least three have done so!

AESGP willing to continue monitoring…and to do its utmost so that it remains a non-issue!

Jacques Morénas provided an Inspector's view of Quality by Design, 5 years after its introduction

He recognised the challenge for regulators and industry to understand and implement this concept, but observed that the 5 years saw:

- How confidence between regulators and industry is beginning to grow
- The interest to better define concepts already existing but without common understanding and way to use
- The shared will to work together from virtual concepts to practical implementation till the end of the process
- The strong wish to facilitate innovation and envisage "regulatory flexibility" within the common interest of protecting patients and public health.

Any Other Business

Representatives from EFPIA questioned whether in future they would have the resources to prepare papers for this meeting, but it was noted that the other interested parties present all considered that the meeting had considerable value and provided an essential opportunity to help in the preparation of realistic guidance to the Industry.

Report prepared by *John Jolley*

PHARMACEUTICAL FORUM

The following questions and responses are a recent selection of those published on an open online discussion group www.pharmweb.net/gmp.html. The Forum serves as a means of exchanging views on international regulations affecting the pharmaceutical industry. Readers are invited to contribute to the Forum by sending their Q&As to **www.pharmweb.net/gmp.html**.

Validation of AHU

Q How is the validation of an Air Handling Unit (AHU) carried out?

Response 1 – Validation (PQ) of AHU is carried out by performing the following tests.

1. Temperature/RH and pressure differential
2. Air flow rate and air changes classification
3. HEPA DOP test (Leak Test)
4. Particle count – viable and non-viable
5. Recovery study
6. Smoke study for air-flow pattern

The tests mentioned above are part of performance qualification.

A well qualified AHU shall be supported with URS/Functional and Design specifications (DQ), IQ and OQ as well.

Response 2 – I think your expectations from Air Handling Unit (AHU), are somewhat over the top. The AHU provides pressurized air at a specified flow, temperature and sometimes humidity. It does not have anything to do with particle count (that is down to the room inlet HEPA filters). And it has nothing to do with DOP testing (that is used to verify HEPA filter integrity). The filters in the standard AHU are bag filters of a grade sufficient to ensure external debris is not drawn into the system (they are monitored by measuring the differential pressure drop across the filters, then cleaning them or sometimes changing them).

Room Air Flows Patterns are achieved through room filter positioning (establish in early design studies). Room change rate and differential pressures are a function of room filter and damper settings.

The AHU is a straightforward piece of equipment to validate and is normally validated as a separate entity. Since one AHU is often supplying air to several rooms all with perhaps a variation in their requirements, it is often the norm to use the AHU to roughly condition the air, then to use a room entry heater and de/humidifiers to attain the exact air requirements.

Response 3 – An AHU is not to be validated because, being equipment, an AHU is to be qualified. What is validated is the result of the air ventilated in the rooms: quantity and quality of the conditions obtained.

Quality equivalence after a process change

Q Are there any guidelines about quality equivalence in order to evaluate a change in an API process? Which parameters should be demonstrated to be the same?

Response 1 – One of the most important factors is that the API produced by the new and the old process should be equivalent – chemically and physically (including polymorph), including related substances and residual solvents.

Response 2 – It all depends on the individual process; you will need to perform a quality risk assessment on what impact the change could have on the parameters and set some acceptance criteria for performing additional testing – if appropriate.

Response 3 – A previous correspondent mentioned the need to pay attention to polymorphism to assess the quality equivalence after a process change. Do you think that polymorphism is a relevant characteristic for an API intended for parenteral use after a lyophilization process? It means that the API will be in solution before the lyo process. Of course the stability, may be relevant.

Response 4 – There was no mention of the intended use of the API or the dosage form in the original posting. Polymorphism might still be important if this could affect the preparation of the solution that will be lyophilised. If it does not affect the solubility/solution process then it will be less important.

Impurities/related substances/degradation product profile, stability and residual solvents levels will still be of relevance.

Grandfather drug management

Q We all know that some very old drugs have "grandfather" status. What is the attitude of the FDA and EU towards them?

Response 1 – If a drug product was on the market prior to the 1938 Act (see 21 U.S.C. 321 (p) (1) and which contained in its labelling the same representations concerning the conditions of use as it did prior to passage of that Act, it is not considered a new drug and therefore is exempt from the requirement of having an approved new drug application.

Under the 1962 grandfather clause, the Act exempts a drug from the effectiveness requirements if its

composition and labelling has not changed since 1962 and if, on the day before the 1962 Amendments became effective, it was (a) used or sold commercially in the United States, (b) not a new drug as defined by the Act at that time, and (c) not covered by an effective application.

The two grandfather clauses in the Act have been construed very narrowly by the courts. FDA believe that there are very few drugs on the market that are actually entitled to grandfather status because those currently on the market are likely to differ from the previous versions in some respect, such as formulation, dosage, strength, etc. If a firm claims that its product is grandfathered, it is their task to prove that assertion.

Finally, a product would not be considered a new drug if it is generally recognized as safe and effective (GRAS/GRAE) and has been used to a material extent and for a material time.

As mentioned above, the Agency believes it is not likely that any currently marketed prescription drug product is grandfathered or is otherwise not a new drug. However, the Agency recognizes that it is at least theoretically possible. In light of the strict standards governing exceptions to the approval process, it would be prudent for firms marketing unapproved products to carefully assess whether their products meet these standards.

Finished product analysis

Q Which stage of product should be considered as finished product in the case of a solid oral dosage form tablet, whether uncoated/coated tablets or packed? If product it coated and analysed at coated stage, is it necessary to analyse again after packing since there will not be any physical change in product? What are the industry's standard practices?

Response 1 – Complete analysis on bulk finish (before strip/blister/bottle packing) is generally followed. Additionally, packed samples should be subjected to an identification and bioburden tests. The hold time of bulk finished tablets must also be established.

Response 2 – The stage after which processing can be said to be finished is packaging, when the product goes into safe storage mode. My opinion is that a sample shall be tested/studied after primary packing, not only for chemical tests but also for microbiological tests.

Response 3 – There are no fixed rules for such cases. In general, once the complete analysis is done at tablets stage (coated means after coating) only nominal tests like description and pack details can be done after packing, when the batch can be released. This is a widely followed practice. But if this is not acceptable, complete testing should be done after packing. In spite of this, many companies follow the first option which is a widely accepted practical approach.

Cleaning validation – 10 ppm criteria

Q My query is regarding 10 ppm criteria applied during cleaning validation of any drug product. Should 10 ppm criteria be calculated considering the entire batch size of drug product, including API and its excipients, or I should consider API input alone for that?

Response 1 – It is my understanding that the batch size means the smallest batch size of the product and it refers to the whole formulation: API and all its excipients.

Response 2 – Cleaning validation is generally directed towards API and not excipients. It is API which you don't want to cross-contaminate with other products, as it could lead to undesirable side effects. The excipients would not be expected to have any clinical effect on patients, so all the limits are for API only.

Drying ovens

Q I have to do the performance qualification (PQ) of a drying oven and I don't know if it is necessary to verify the temperature inside the product loaded on the trays of the dryer. If the answer is yes, how can I establish the temperature specification?

Response 1 – It is well to remember that validation of equipment is required to validate the process the equipment is used for, ie. your drying process must be validated. The process developers would have dried the product at various temperatures over various times, until they arrived at a combination that gave the degree of dryness they required.

So the answer to your question lies with this process – exactly what does the process require you to do? You can then decide on equipment tests that will validate that the heat treatment of the product is compliant with the requirements.

For example, the process calls for the product to be subjected to a temperature of 50°c for one hour, you must verify that the temperature throughout the oven is as specified and that the time as specified is accurate, and both are consistent. If an actual product temperature is stipulated (as it might with a fluid) you must verify through your validation process what oven temperature will give you that product temperature. This is assuming you cannot monitor the actual product temperature during processing.

DATES FOR YOUR DIARY

FEBRUARY

23-24 February 2011 – Barcelona, Spain
Revision of bioequivalence requirements for modified release products
www.eufeps.org

28 February – 1 March 2011 – Amsterdam, The Netherlands
Pharmacovigilance and risk management 2011
www.iqpc.co.uk

MARCH

1-3 March 2011 – Manchester, UK
Preparing for the future
www.nsf-dba.com

2 March 2011 – London, UK
Personalised medicine – the evolving regulatory landscape
www.mhra.gov.uk

2-4 March 2011 – Berlin, Germany
The 5th annual front end of innovations® Europe
www.iirusa.com/feieurope

6-10 March 2011 – Strasbourg, France
Hybrid materials 2011 – Second International Conference on Multi-functional, Hybrid and Nanomaterials
www.elsevier.com

9 March 2011 – Manchester, UK
Pharmaceutical Legislation Update
www.nsf-dba.com

8 March 2011 – London, UK
The annual discussion meeting with the MHRA for QPs, QA Managers and their colleagues
www.pqg.org/events

14-15 March 2011 – London, UK
Pharmacovigilance
www.smi-online.co.uk

24 March 2011 – London, UK
Counterfeit medicines: the regulatory and industry challenges
www.jpag.org

30-31 March 2011 – London, UK
Controlled release: scientific progression and commercial opportunities
www.controlledrelease.co.uk

APRIL

5 April 2011 – London, UK
12th Joint Conference on the Qualified Person: Professional Development Symposium
www.rpharms.com

6 April 2011 – London, UK
Meeting the counterfeit threat
www.smi-online.co.uk

6-7 April 2011 – Nice, France
BioProcess International Europe
www.informaglobalevents.com/events/bpi1

13-14 April 2011 – London, UK
Asthma & COPD
www.smi-online.co.uk/goto/asthma-copd.asp

13-15 April 2011 – Heidelberg, Germany
Pharmaceutical packaging materials conference 2011.
Part I: printed packaging materials &
Part II: plastic packaging materials
www.gmp-compliance.org

MAY

10 May 2011 – London, UK
Joint meeting with BARQA on Investigational Medicinal Products
www.pqg.org/events

11-12 May 2011 – London, UK
Generics, Super-Generics, and Patent Strategies
www.generic-pharma.co.uk

12 May 2011 – Lugano, Switzerland
Symposium on Pharmacovigilance
www.afti.ch/allegati/Farmacovigilanza2011.pdf

JUNE

13-17 June 2011 – Prague, Czech Rep.
PharmSciFair
www.pharmscifair.org