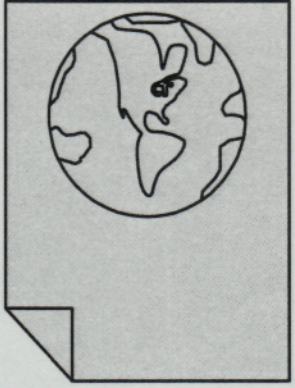

TECHNOLOGY TRANSFER IN PRACTICE

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Technology Transfer Validation in Practice

Preface

There can be few pharmaceutical companies over the last 15 years that have not undergone the maelstrom of take-overs, mergers, downsizing, centres of excellence or product rationalisation. All these events can, and frequently do, result in product or products being transferred between manufacturing sites. At best it will be a product or product type that the receiving site is familiar with, or at worst, one with which they are totally unfamiliar.

The challenges to effect technology transfer in a timely fashion, within budget and achieving savings that have probably been pre-commirted, at the requisite quality are approximately the same for each aspect.

This guide provides a "ready reckoner" of the issues to be considered to achieve these objectives, ensuring that the regulatory issues from both a licensing and inspection perspective are addressed, and maintaining the organisation's integrity for its products and with its shareholders.

In considering the technology transfer process reference is made to the situation within the European Union (EU) in the main; however, where useful guides or proposals are available from other regulatory authorities, notably the FDA, these have been included for completeness.

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October 2002

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Stewart Green and Paul Warren

1 PURPOSE

The purpose of this guide is to present both an overview of the technology transfer process and to offer specific guidance concerning the key aspects of product transfer management, and how to document outcomes to completely satisfy both internal requirements and regulatory expectations. We provide suggestions on the personnel to be involved in the process, and a checklist to serve as an *aide memoire* to ensure that key steps have been covered.

2 SCOPE

This guide discusses the principles behind the technology transfer process, which can be applied in full or in part, dependent on the nature and complexity of the products involved in the transfer. The requirement to perform a formal technology transfer is prescribed - directly and indirectly - by the regulatory authorities within the European Union (EU). For those markets regulated by the Food and Drug Administration (FDA) in the United States, there are very specific requirements for transfer. Whilst this guideline is focused on the EU, the principles, if applied in full, would be expected to meet FDA requirements also.

3 THE TECHNOLOGY TRANSFER TEAM

The decision to transfer products between manufacturing sites is frequently driven by economics. This may be the result of a global product or site rationalisation programme, or it maybe driven by attempts to consolidate similar product types at a single site. It may result from a merger or take-over, which generates excess capacity in the supply chain leading to consolidation. Whichever the key driver for transfer, it is likely that due to the sensitive nature of the proposals, both in terms of affected sites and shareholders' confidence, the intention cannot be shared with the affected sites until timescales are already tight. It is against this background that the team responsible for the transfer process is required to operate. It must be accepted that although not ideal, this is an understandable consequence of operating in a highly competitive global business.

The structure of the validation team will depend on the degree of fit of the transferred product with the local site capabilities. For example, if the recipient site has a known expertise in solid dose formulations and the transferred product is a straightforward tablet formulation then the team members will be drawn from Quality Control (QC); Quality Assurance (QA) and Production (or Process Support where this facility exists). If however the product represents a change in complexity (e.g. sustained release formulation) or a change in product type (e.g. capsule formulation where the site has previously only made tablets), then the core team may need to be enhanced *by* the inclusion of engineering personnel.

Other disciplines, for example the training function, need also to be considered. li there is a major impact on site quality systems and/or personnel knowledge base, then extensive training of site personnel throughout all disciplines, but particularly operations personnel, needs to be considered. It is unlikely that the training can ever supplant the collective knowledge of the donor plant, but all training should seek to identify key gaps in the process between donor and recipient plants; and deliver a training programme to close such gaps.

In many situations the timescales will preclude all team members being full time on the process, unless an organisation is specifically resourced to provide this service.

However, it is essential that at least one member is full time and has specific responsibility for the project. Their role may be project management, co-ordinatory. or "hands on" in the process environment but they must be focused and not distracted by the pressures of a "day job".

A regulatory interface is also an essential requirement. Despite a supposedly uniform regulatory environment in the EU, the reality for most companies is that even for a single product there maybe divergent regulatory requirements; indeed the producl registration may not be common to all markets and therefore the impact of change will also be variable.

The responsibilities for each team member need to be defined at the outset, so that all the bases are covered and all members understand what is expected of them.

PROPOSED TEAM MEMBERS AND RESPONSIBILITIES

Team Member	Responsibilities

Process Technologist	• Central focus for transfer activities
	• Collates documentation from donor site (see Section 4.4)
	• Performs initial assessment of transferred project for
	  •feasibility
	  •compatibility with site capabilities
	  •establishes resource requirements

QA Representative	Reviews documentation to determine compliance with Marketing Authorisation (MA) Reviews analytical methods with QC to determine capability, equipment training requirements Initiates conversion of donor site documentation into local systems/ format Initiates or confirms regulatory requirements, e.g. change to manufacturing license; variations to MA if process changes needed, etc.
Production Representative	Reviews process instructions (with process technologist) to confirm capacity/capability Considers any safety implications, e.g. solvents; toxic; sanitising materials Considers impact on local Standard Operating Procedures (SOPs) Considers training requirements of supervisors/operators
Engineering Representative	Reviews (with production representative) equipment requirement Initiates required engineering modifications/change/part purchase Reviews preventative maintenance/ calibration impact, e.g. use of more aggressive ingredients; more temperature sensitive process, and modifies accordingly

4 TECHNOLOGY TRANSFER: KEY ACTIVITIES

4.1 Timelines

As previously indicated, the timelines for the transfer may well have been pre-ordained by financial/marketing considerations. The first key activity of the team is therefore to do a "sanity check" to determine at the macro level whether or not those expectations can be met. If not, then senior management must be informed to ensure

that the implications on the donor site (which may be closing), the recipient site (whose budget may have assumed the transferred volume) market supply, stock market confidence and so on, can be considered. The other time driver may well be the regulatory aspects (considered in Section 4.2).

At the initial stages the team will have to make a number of assumptions. For example, it will be assumed that process validation, analytical validation and cleaning validation are trouble-free. It will be assumed that actives, excipients and packaging components are available on standard lead times. A complete time and event schedule at the macro level should be constructed on these assumptions working backwards from the proposed transfer deadline. Key stages of the process such as:

data collection
data review
regulatory impact with particular emphasis on any change approvals
analytical validation
pilot or full scale process batch
stability set down (if required)

should be mapped to determine whether the predetermined transfer timelines can be met.

4.2 Regulatory Issues

Changes to the approved Marketing Authorisation (MA) can represent the greatest challenge to the transfer timelines. Most manufacturing units no longer supply a single market, and particularly where centres of excellence have been created, a single unit may supply on a global basis. For even a simple activity, registering a site change for example, the regulatory process can vary from 30 days to 12-14 months. This is why an initial regulatory assessment is so important in determining whether the overall timelines can be met.

Fundamental to the transfer process is the decision to implement little (if any) change in the transferred product/process. As the level of change increases, so does the regulatory complexity and the associated timelines. Guidance is available in assessing change in both of the major regulated markets, i.e. FDA and EU.

The FDA has published a series of proposals under the simplification process, for example SUP AC (Scale Up and Post Approval Change) Guidance for Industry for Solid Dose Forms.

These provide guidance covering advice on so called "like for like" changes, i.e. the substitution of one granulator for another. A brief resume of some changes considered is given at the end of this section. By using this guidance it is possible to minimise the regulatory impact in those markets governed by the FDA.

Similarly, within the EU, at least for nationally registered products, guidance notes are provided for not only the type of change and its regulatory approval time, but also for the information required to support the change. Changes are divided into 30+ so-

called Type 1 variations covering diverse changes ranging from change of site to changes in analytical methods and other more complex variations, so-called Type 2 changes. In theory a Type 1 variation is approvable within 30 days and a Type 2 variation within 90 days. In practice only some member states of the EU achieve these approval timelines. As before a resume of the changes and their requirements is given at the end of this section.

EU GUIDELINE ON VARIATIONS TO MARKETING AUTHORISATIONS
(The full transcript can be found in *The Rules Governing Medicinal Products in the European Community, Volume 6A: Notice to Applicants, Chapter 5: Variations.}*

Nature of Change	**Documentation Required**
1 Change of manufacturing site	• No change in process, specifications or test methods • Proof that proposed site is authorised for the dose form production ("manufacturing licence") • Declaration in writing of no changes in previously approved specification • Batch analysis comparison; at least one full size batch, and two pilot batches compared with three full-scale from previous site
Replacement of excipient with comparable excipient	• No change in dissolution profile for a solid dose form • Justification for change including stability impact • Commitment to provide ongoing stability and three months' data available up front • Comparative dissolution profiles of "old" versus "new" product • Declaration of no change in release or shelf life specifications
Qualitative change in composition of packaging material	• Justification for change including comparative data, e.g. permeability • For semi-solids and liquids proof of no interaction between container and product • Validation of any analytical methods used to control packaging material . Ongoing stability and three months data available up front • Declaration of no change in release or shelf life specifications

11	Change in manufacturer of active substance	The specifications, controls and synthetic route should be the same as already approved (or minor changes justified) Batch analysis of at least two lots from new source Declaration by the MA holder that there are no changes in finished product specifications
15	Minor change in manufacturing process of product	Product specifications not affected Dissolution profile for one "new" batch compared with three "old" batches (solid dose) Justification for not submitting a new bio-equivalence study
25	Change in test procedures for product	Appropriate validation data for analytical method and comparative data between "old" and "new" method Declaration that release and shelf life specifications remain unchanged
30	Change in pack size for the product	Declaration that specifications are unaffected Justification that new size is consistent with dose regime Declaration that container properties are unchanged Declaration that stability studies will be conducted

NB. Only a selection of the 34 categories of change have been provided; the number is that used in the Variations.

FDA GUIDANCE FOR INDUSTRY: Changes to an Approved New Drug Application (NDA) or Abridged New Drug Application (ANDA)

Changes Requiring Prior Approval

Move to a different manufacturing site when the new site has not been inspected by the FDA for the types of operation proposed
Move to a different manufacturing site when the new site does not have a satisfactory Good Manufacturing Practice (GMP) inspection for the operation proposed
Changes that may affect the controlled release of the dose delivered to the patient
Changes in sterilisation method for a sterile product
Changes in a viral removal step

Changes from dry to wet granulation or vice versa
Changes in synthetic route for drug substance
Addition of an ink code imprint to a solid dose form
Relaxing an acceptance criteria
Deleting a specification
Establishing a new analytical procedure
Changes in the immediate packaging material

Changes Which Can be Implemented in 30 Days if No Adverse Comment

Moves other that those requiring prior approval
Moves of testing to another site
Changes in manufacturing process other than those requiring prior approval
Changes to aseptic filtration parameters
Changes from one sterilisation autoclave or oven to another
Relaxing an acceptance criteria or deleting a test for a raw material
Change in an analytical method for a raw material
Change in size of a primary container
Addition or deletion of a desiccant
Reduction of an expiration date to provide increased assurance of identity, strength or purity

Changes Which Can be Filed in Annual Report

Move to a different site for secondary packaging
Move to a different site for labelling
Changes to equipment of the same design (see SUP AC guidelines)
Change in the order of addition of ingredients for a solution
Changes in specification to comply with *United States Pharmacopoeia* (USP)
Tightening of specification
Change in container closure system for a solid dose form, e.g. adding a child resistant closure; change from one plastic container to another of same type

NB. Similar guidance for FDA regulated markets for making changes to NDA or ANDA. As for the EU guideline, only a selection of changes has been given.

SUP AC (Scale Up and Post Approval Changes) Guidance for Industry for Immediate and Modified Release Solid Oral Forms (FDA)

Operation	Equipment Type	Examples Considered Essentially Similar
Milling	Fluid mill	Tangential jet Loop Opposed jet Fluidised bed
	Impact mill	Hammer air swept Hammer conventional pin/disk

Blending/mixing	Diffusion mixers		"V" Blender Double cone blender Slant cone blender Cube blender Bin blender
	Convection mixers		Ribbon blenders Orbiting screw blenders Planetary blenders Vertical high intensity mixers
Granulation	Wet high-shear Granulator	Vertical	Horizontal
	Wet low-shear Granulator	Planetary Screw	Kneading
	Extension granulator	Radical Axial	
			Ram Roller or gear
	Fluid bed		All types
Drying	Direct heat, solid bed		Tray and truck Belt
Dosing	Tablet press		Gravity Power assisted Centrifugal Compression coating
	Encapsulator		Auger Vacuum Vibratory Dosing disk Dosator

NB. This guidance note provides guidance on what types of equipment can be considered essentially similar for each stage of the manufacturing process. Again only a selection has been given.

4.3 Determining the Process Scope

As previously stated the ideal situation is to simply transfer the total process without change from the donor to recipient site. In practice this is seldom straightforward. During the initial feasibility assessment the comparability achievable is evaluated. Careful comparisons of processing equipment including the sophistication of the

control mechanisms available, analytical capability, impact on other site processes, e.g. cleaning validation complexity, training and documentation requirements all need to be factored into the process scope.

Excipients may not be available from the same source or the receiving site may have different preferred suppliers. Actives are normally sacrosanct, although in some cases even this change may have to be made because of other legislation, e.g. restrictions on cross-border trade in controlled drugs.

When all unavoidable changes have been identified then the scope of the transfer must be carefully formalised so that all involved parties are aware of the work involved.

4.3.1 Managing Change

Following the scope determination, the work needed to support any of the identified changes must be formalised. A single example will provide an illustration. Say for example, it has been necessary to change the source of an excipient. The following list of questions, although not exhaustive, should be posed.

> Is the source of the excipient declared in the marketing authorisation? If so, regulatory action may be required.
>
> Do the routine quality control tests provide sufficient control to characterise the practical use of the excipient? For example, is the particle size, shape or distribution important?
>
> Are there any known interactions of the excipient in the formulation which may be pronounced with the proposed source?
>
> Are there any known interactions of the excipient with the container/closure system?
>
> Have any lots of donor site excipient been rejected and, if so, did this have any impact on the specification?
>
> Do both sources have European Certificates of Suitability, which would indicate that they are equally well characterised by the pharmacopoeial tests?
>
> Is the manufacturing process for the proposed excipient significantly different such that it may pose different problems (e.g. presence of solvents where previously none were used, aqueous based extraction which may lead to higher bacterial/fungal counts)?
>
> Is the proposed excipient available in manageable quantities (e.g. lifting restrictions may require availability in no more than 25 kg quantities)?
>
> Can it be assured that the proposed excipient will not interfere in the finished product analysis (particularly HPLC)? (A minor related substance may co-elute with the active product.)

As can be seen from the previous list, even what on the face of it may be a simple change, can and does involve complex issues.

4.4 Documentation

In order to maximise the chances of transfer success, as soon as dialogue between donor and recipient site can take place then the team should start to assemble available documentation. It is difficult to provide a definitive list of requirements as this will vary from product to product, process to process, and site capability to site capability. However, as a guide the following should be assembled:

- *Production master formula*

  This should be compared to the formula actually dispensed and to that in the MA. It is not unheard of for differences to be seen.

- *Manufacturing instructions*

  These should be compared to those in the MA. In our experience, for older products the detail is likely to be minimal (e.g. granulate the ingredients and tray dry to a predetermined moisture) and differences between actual and licensed can usually be accommodated. For recent products the detail may be substantial (e.g. granulate in a high-shear mixer using both granulator and chopper blades operating a high speed for 30 minutes) and changes require regulatory activity.

- *Process validation studies and/or process development studies*

  These will provide valuable insight into process robustness, impact of variables on finished product quality, critical control points, etc.

- *Rejects/deviations*

  Again these will indicate process robustness; determine whether manufacturing instructions contain the correct level of detail and whether the donor reacted appropriately to the failures.

- *Analytical methods/validation*

  These should be compared against the MA with particular emphasis on the finished product specification. It is worth remembering at this point that the MA may vary in this and all other respects from market to market.

- *Raw material specifications with particular emphasis on the active and key excipients*

  The latter may be of particular importance in modified release formulations. Care must be taken with any animal delivered products in the current climate of enhanced concern with transmissible spongiform encephalopathy (TSE).

Certainly within Europe or where product is likely to be exported outside of the EU, most regulatory authorities will look for the absence of potentially compromising material. If it is recognised that product still contains material of bovine, ovine or caprine origin (e.g. magnesium stearate), it would be as well during the transfer to substitute a vegetable equivalent. This is one case where like-for-like transfer should be avoided.

- *Packaging components specifications*

Again these should be compared against those in the MA and the specification should be as comprehensive as possible, particularly as the materials of construction of bottles, plastic tubes, laminates, etc. may well be commercial preparations for which equivalency is potentially difficult to establish.

- *Safety data*

Particularly where a material has specific safety issues (eg, irritant or potent sensitiser, solvents, etc.) then all relevant data on handling requirements, disposal, environmental impact, safety data sheets, etc. should be collated.

- *Other data which may provide a valuable insight into the robustness of the product and the production process*

These include analytical deviation reports and customer complaints.

- *Where a number of products are to be transferred*

The collation of this repository of information may assist in the prioritisation of the transferred products. Choices can be made on degree of difficulty; regulatory issues and the timelines involved; purchasing timelines/sourcing difficulties, and so on.

- *It should be remembered that, where transfer results from the donor site closure, particular sensitivity is needed when dealing with the collation and evaluation of the information. Now is not a good time to be critical of the donor site practices and procedures!*

4.5 Validation

This is one of the most critical issues in the technology transfer process because it frequently determines the complexity of the process and it is a focus for the regulatory agencies; not only from the licensing side but also during inspections.

The approach to validation for any transferred product must always be documented and science based. A number of regulatory guidelines are available: however, they are just that - guidelines. Of necessity they must deal in generalities. It is up to the receiving site team to evaluate each product and the information portfolio, and to determine the level of validation required. In the context of the transfer process we are usually talking about process qualification (PQ), unless of course equipment

changes are also involved, in which case installation qualification (IQ) and operational qualification (OQ) may also be needed. Pragmatism also has a place in the decision making process. For example, if the product being transferred is a simple liquid in which actives and excipients are dissolved by simple agitation; if the equipment in donor and recipient plant is the same or essentially similar; if no changes in source or type have been made to excipients and actives and if the analytical methods are direct from a major pharmacopoeia, then it may be decided that no prospective validation is required and the transfer success will be measured by ongoing monitoring of the product.

There are usually three separate validation activities, which we shall consider in turn, namely process validation, cleaning validation and analytical validation.

Serious consideration should be given to the merits of running a pilot scale (say 10% normal lot size) or even placebo product, if the evidence gathered during the transfer process suggests that the product may be complex or difficult to transfer/validate. This has three advantages. Firstly it allows all personnel involved to gain some familiarity with the production methods. Secondly, it may help to avoid costly "write-offs" and thirdly, by working outside of the formal validation protocol, it provides an opportunity to address the issues without compromising the validation protocol or invoking a complex formalised investigation, in the event that something goes wrong.

4.5.1 Process Validation

Process validation has probably consumed almost as much time, energy and money in the pharmaceutical industry over the last 10-15 years as manufacturing commercial product! Many companies also appear to have lost sight of the purpose of validation. In some circumstances, validation *appears* to be performed for the benefit of the validation department or, worse still, the regulatory agencies.

There is only one reason to validate a process. That is to *secure* the manufacture of a product, so that it can be *guaranteed*, with a high degree of probability, that the *patient* receives product of the requisite safety, quality and efficacy each and every time. It also makes good business sense to be able to quickly and reproducibly release good quality products.

The approach to process validation, as previously stated in the introduction to this section, will vary with product type and complexity. We will concentrate on the most common dosage forms, as discussion of the transfer of technologically sophisticated products such as inhalation aerosols, steriles, transdermal patches etc., is best dealt with in a special treatise. As with most validation, three successive and successful repetitions of any of the validation processes given below are the norm.

4.5.1.1 Solutions

The key to validating solutions is to ensure that:

(i) raw materials specifications for actives and excipients exercise control over critical parameters such as particle size, particle shape, particle size distribution and solubility, and

(ii) the manufacturing process parameters, be they temperature, order of addition or agitation, are controlled and monitored to effect consistent dissolution of the ingredients.

Once such controls have been established then process validation can usually be effected by monitoring the active content of the individual filled containers produced throughout the filling period.

4.5.1.2 Creams

Creams may involve solubilisation of the actives in either the water or oil phase, or dispersion without solubilisation of the active in the water or oil phase. Where the actives are dissolved or dispersed during the cream formation, the energy involved to effect the formation of the oil/water micelle is such that homogenous distribution is almost assured. If the active is dissolved or dispersed after cream formation, this is likely to be a lower energy process and homogenous distribution through the viscous substrate maybe more difficult.

In the former case, validation can be affected as for liquids by careful control of the physical attributes of the actives, in particular particle size distribution, and by careful control/monitoring of the homogenisation conditions. The active distribution can then be monitored during the filling process by assay of individual filled units.

In the latter case, where distribution is effected after cream formation, then active ingredient distribution will normally be monitored at the bulk stage, taking samples throughout the blender as well as the filled units. The purpose of the blender samples is to determine whether the blending plateau is achieved under the prescribed conditions, i.e. the active has been evenly mixed.

Sampling of bulks can be technically very difficult: even the introduction of the sampling device may disrupt distribution of the active, although this is less likely in a viscous substrate than in a free-flowing powder (see Section 4.5.1.4 on solid dose forms). The sampling regime is to some extent dependent on the blender type, but commonly a matrix of samples is taken by dividing the bulk into top, middle and bottom layers vertically and side - middle - side horizontally.

4.5.1.3 Ointments

Ointments pose similar if potentially more challenging problems than creams. Normally the active is distributed, not dissolved, unless it is reasonably heat stable when it can be dissolved at the molten "fats" stage. As ointments are generally relatively viscous, but due to the lack of water can be blended aggressively without fear of "cracking", i.e. separating phases, then the actives are usually incorporated using some form of high shear mixer. The degree of difficulty of doing this is to some extent dependent on whether the active can be incorporated either when the fats are molten or when they are cool. For the former, distribution should be relatively straightforward; for the latter, the viscosity may demand vigorous or prolonged mixing. Validation sampling is as for creams, i.e. bulk and filled units.

4.5.1.4 Solids

Validating solid dose forms after transfer has generated significant debate with the industry and its regulators as to the complexity of the validation process. There are probably several reasons for this as follows:

(i) The multistage nature of the typical solid dose process, e.g. sieving, mixing, granulating, milling, drying, compression and coating.
(ii) The low level of active in the typical tablet.
(iii) The impact changes or variations in the manufacturing process have on disintegration and/or dissolution and hence possibly bioavailability.
(iv) As in most cases the active is not dissolved in the substrate, distribution is accomplished by physical dispersion only.

In the USA the FDA has insisted on blend uniformity studies, even to the extent of requiring them as routine. Within the EU the regulators do not have a declared policy and are driven by good science; normally this requires blend uniformity studies on validation only. A number of companies have taken such studies to extremes and have performed blend studies at every stage of the solid dose process.

This is probably reasonable at the development stage of a product to demonstrate exactly when and under what conditions the mixing plateau, i.e. the point at which the active is homogenously distributed, occurs and to ensure that subsequent de-mixing does not happen. However, for a previously manufactured product, particularly one for which a large number of lots have been manufactured, consistency of the finished product results should provide a reasonable indication that the process is under control; hence blend homogeneity and finished product homogeneity studies only are required.

Sampling at the final blend stage poses particular problems when powder sampling; the introduction of a so-called sample "thief has been shown to disrupt mixing. Multipoint sampling throughout a blender is normally used, sampling wherever possible a sample size equivalent to the final dose form weight. The regulatory authorities (predominantly the FDA) will accept sample sizes up to three times the dose weight, but even this size is difficult to sample consistently.

Most granulates consist of granules/powders of different flow indices, which upon the introduction of a multipoint sampling device can differentially flow into the sample cavity, leading to apparently heterogenous samples. Even the angle of introduction of the "thief can impact on the sample characteristics.

Final product sampling is usually performed by taking compressed tablets throughout the compression run. Variables that need to be considered are interchangeability of compression machines to provide production flexibility; the impact of the change of overhead feed drums and whether segregation occurs as the drum/hopper empties; the impact of compression machine speed on dose reproducibility; the impact of vacuum transfer parameters such as velocity, fluidisation air volumes; etc. Direct compression formulations can be more problematic than wet granulation formulations as the incorporation of active in the former is physical only.

Each formulation transferred should be considered on a case-by-case basis to determine the most appropriate validation approach. It may be appropriate, if time and economics permit, to manufacture a 10% scale pilot batch with additional sampling to gain an understanding of the manufacturing dynamics before resource is committed to a full-scale batch.

4.5.1.5 Acceptance Criteria

It is difficult to set general acceptance criteria for each dose form as it is dependent on so many different factors. However, as a guide the following criteria have gained acceptance within the industry and with the regulatory authorities.

For a *tablet product* the criteria outlined in the United States Pharmacopoeia *(USP)* for uniformity of dose should be applied, but the relative standard deviation (RSD) should not be greater than 5.0%. If it is wished, during routine manufacture, to control content uniformity by weight, it will be necessary to demonstrate a closer relationship of weight to content. It is unlikely that this may be assured with a RSD greater than 3.0%.

For *liquids, creams , ointments and gels* it is normal to take samples at several stages during the production process. The sampling points are dependent on the complexity of the manufacturing process and the mechanics of incorporation of the active. For example, if there are several aggressive mixing stages in the process it may be possible to only sample at the end of the process; for a more gentle process it may be necessary to demonstrate homogeneity at several steps.

For *intermediate* stages acceptance criteria using a 95% two-sided confidence interval about the mean could be used which would ensure that the true batch mean is contained within the data with 95% confidence. The calculation:

$$X +/- T_{df,0.025} S\sqrt{n},$$

where X = meanofn values
S = standard deviation of n values
n = number of unit samples
df = n - 1
to.o25 = 97.5 percentile of the t distribution with df degrees of freedom.

For final product it is normal to expect all finished product samples taken throughout the filling run to meet in full the finished product specification

4.5.2 Cleaning Validation

This is another area in which careful risk assessment is required when transferring products.

As a practical example, the receiving site is used to dealing with fairly innocuous solid dose forms and then has to manufacture a tablet containing highly potent active. It is quite possible that - based on the normal criteria used to assess cleaning efficacy

(less than 0.1% of the standard daily dose of the "contaminant" present in the daily dose of the recipient product) - local cleaning methods will prove inadequate.

Consideration would need to be given to either:

(i) re-evaluating the cleaning methods, which might be an onerous task requiring extensive revalidation;
(ii) assessing whether a change in detergent might be sufficient to effect removal; or
(iii) whether a facility would need to be dedicated to the new product.

Similarly, if the receiving site was used to handling creams and then had to deal with a fatty ointment, once again current cleaning methods may prove inadequate.

Depending on the status of the donor plant, analytical methods may or may not be available which are sufficiently sensitive to detect around the parts per million rate, and this method development will need to be factored into the timelines.

Finally, a new product may bring with it additional microbiological demands, e.g. products containing natural ingredients, high sugar concentrations, poorly preserved, and so on. This will probably need the services of a competent microbiologist to assist in the risk assessment.

4.5.3 Analytical Validation

The technology transfer of analytical methods can almost be considered as a project within a project, in that the ideas and thinking behind the overall product transfer apply equally to the analytical area.

All relevant documentation, method validation reports, out of specification reports, laboratory investigations and typical analytical results, should all be reviewed by a transfer team. This transfer team should consist of all parties who will be using the methodology, and should include a minimum representation from all those involved in routine testing, stability and process validation support, plus at least one knowledgeable individual from the donor site, when possible.

Each test should be reviewed against its history in the hands of trained analysts, the skill set of the receiving site, and the sophistication of the methodology.

In addition emphasis should be placed on site-specific operating procedures, to highlight ways in which differences could impact the way the test is implemented at the respective sites.

A record of the rationale used to decide on the level of technology transfer necessary for each test should be made at this stage. The preparation of a Validation Master Plan (VMP) may prove a useful vehicle in which to record these decisions.

Guidance on the level of technology transfer necessary for specific test procedures is given in the IPSE guidance on technology transfer. However, recommendations on

some of the more common test requirements as applied to common pharmaceutical formulations are detailed below.

4.5.3.1 Assay

Should always be transferred although matrixing can be used on similar formulations. Typically this will be carried out by two analysts at each site, in triplicate, on three batches, on three different days. The analysis should consist of independent preparation of reagents, standards, etc. and should use different batches of analytical columns if appropriate. During the analysis any standard system suitability tests must be met and the acceptance criteria are usually based on the mean assay and variability obtained together with a visual comparison of the chromatography. Typically limits of plus/minus 5% of the mean assay between donor and receiving site are considered acceptable.

4.5.3.2 Impurities/Degradants

Should always be transferred. The samples analysed and the analysts used are the same as for the Assay section above. Transfer should also include confirmation of the limit of quantitation and response factors for those substances where quantitation is calculated from the relative response to that of the drug peak. Old samples are often useful in these transfers, especially for products that typically have low levels of impurities.

Acceptance criteria are usually based on mean and variation values (variation may be expressed in absolute rather than relative terms) and a visual comparison of the chromatography.

4.5.3.3 Dissolution

Typically transferred but often limited to one analyst, one batch and a dissolution profile on 12 units at each site. Acceptance criteria are typically mean meets specification with an absolute difference of not greater than plus/minus 5% and profiles are comparable.

4.5.3.4 Identity

Varies widely in techniques and complexity but are typically carried out on one batch only with acceptance criteria based on showing equivalence.

4.5.3.5 Microbiological Testing (including Sterility andLAL)

Transfers are not normally carried out on these test procedures as these are usually subjected to "in house" validation before use. Validation is usually completed in triplicate on three different batches.

4.5.3.6 Compendial Methods

Transfers are not normally considered necessary. However care should be taken; these methods are not always described in sufficient detail to ensure comparable results are

obtained (e.g. column packing details, extraction times etc). If the receiving site has had no experience of the formulation a limited transfer may be prudent.

As with all such guidance different approaches are equally valid, and provided a sound rationale is recorded then this should be acceptable to the regulators.

The conclusions reached should be acceptable to all parties involved but, in general, and in the experience of the authors, this is not always the case. There are a number of pressures present at this time: some subconscious and others more direct. The vast majority are to reduce the workload and speed up the whole process, but it is our experience that more time has been lost through foreshortening of the process, than in carrying out unnecessary additional work.

It is important to remember: this is a knowledge transfer process as much as a technology transfer process.

4.5.4 Protocol

For those methods where a formal technology transfer has been deemed necessary, it is important for the whole process to be recorded in a protocol, prior to any testing being completed. This protocol should ideally be generated by the donor site, since it is considered expert in the methodology. However, alternative arrangements can be made if necessary, but it is preferable that any such protocol be generated by individuals who will not participate in the subsequent analysis.

This protocol should include the following sections:

(i) *Objective* — a clear statement of the objective of the transfer, from which laboratory the method is being transferred and which of the receiving sites' laboratories are included in the transfer.
(ii) *Scope* - a clear statement of the methods being transferred and what is involved in the transfer.
(iii) *Definition of responsibilities* - who is responsible for what and when, e.g. who writes the report, who signs the report, when does responsibility for the method transfer from the donor site to the receiving site.
(iv) *Definition of terminology* — do not make assumptions that everyone has the same understanding of terms used (this is especially important in transfers between different countries).
(v) *Materials, methods, equipment to be used* - should include details on how the transfer analysis will be transferred, define the samples to be used, the number of replicate sample preparations, the number of different analysts, the number of days on which the analysis is to be completed, the number of replicate injections of samples and standards and how they should be treated (individually, meaned, etc.).
(vi) *Pre-qualification activities* - what training, if any, is required to be carried out by staff at the receiving site before the main part of the protocol is executed, what if any trial runs will be completed and what will happen to the results.

(vii) *Experimental design used* - if a number of similar formulations are being transferred at the same time it may be prudent to investigate the potential for reducing the workload by the use of experimental design. If this course is followed the design and the rationale for its use should be included,

(viii) *Acceptance criteria* - detail what acceptance criteria will be applied to which results, include any statistical assessments to be made,

(ix) *Remediation process* - if all goes well this section should not be needed but including it at this stage enables subsequent actions to be more easily justified. It should include details of those involved in any investigations undertaken and any additional training requirements,

(x) *Documentation* - should make reference as to whether the transfer will be completed using the donor site's documentation or whether this is to be converted to the receiving site's format ahead of the transfer work. It should also include how documentation generated during the transfer is identified, handled, reviewed and stored,

(xi) *Raw data* - how is the raw data to be identified, handled, reviewed and stored,

(xii) *References* - references to any external documentation used during the assessment prior to generating the protocol and any site SOPs used during the transfer,

(xiii) *Approval signatures* — who will approve the protocol and subsequent report. Should include name, job function, date and where working across time zones, the time and time zone.

For older products, where validation data to modern standards is not necessarily available, consideration should also be given to revalidating the methodology to International Committee for Harmonisation (ICH) requirements as the movement of the product may open up discussions with the regulators on these aspects of the licence.

Only when this protocol has been agreed should analytical work commence.

When the analytical work is complete there are, in common with other qualification-type work, a number of possible outcomes. Hopefully these and the necessary remediation were included in the original protocols, however for those that were not the normal processes of investigation and further work should be followed.

Do not forget that the underlying reason for the transfer is to ensure that the method is robust, compliant and can be used reliably at the new site.

The outcome of the protocol should be recorded in a formal report, any deviations discussed and justified and the report duly approved by the same signatories.

Depending on the sophistication of the test and the general skill set of the receiving site, consideration should be given to how additional staff will be trained in these new methodologies.

4.6 Packaging Issues

This section will concentrate on primary, i.e. product contact packaging, although the regulatory issues involved in declaring a change of site on label, leaflet or carton can be considerable!

Issues to be considered are (i) availability and (ii) comparability.

Most sites will have a purchasing strategy of preferred suppliers whereby to secure economies of scale, major items will be purchased from a single supplier; bottles and laminates often fall into this category. Wherever possible supply chains will also be kept short, purchasing from as close to the manufacturing unit as possible.

Where product is transferred across countries or continents this may cause conflict between the needs of purchasing and the regulatory position in a product transfer. Significant changes in primary packaging are likely to require at least three months up-front stability and for sensitive products possibly six months at 25°C/60% relative humidity (RH) and 3 months at 30°C/75%RH.

Compatibility may also be an issue on a number of fronts.

First, as the plastic compounds used in both bottles and blister pack laminates are often commercially sensitive, it is sometimes difficult to directly compare them except by resorting to IR trace comparison. Whilst this may provide a chemical compatibility, the bottles or laminates may still have different barrier properties and it may be necessary to compare minimum vapour transmission rates (MVTR) as well.

Second, although not normally considered a problem with solid dose forms, liquid, creams or ointments may need data generated on extractables and there is a potential for migration of the printing inks into the product. Similarly, some products may interact with the container causing discolouration or even cracking.

4.7 Stability Requirements

In the previous sections the need to consider stability for transferred products has been mentioned several times. As previously stated, the best avoidance tactic is to make no changes in either process or packaging components. Practically this can be a difficult position to sustain and in most cases sufficient changes will need to be made which precipitate a stability requirement.

By the time a 10% pilot scale batch has been produced, samples taken (and presuming stability indicating assays are available and validated), three months may have elapsed until the first stability time point; a further one month for results generation/reporting; then a total of at least six months can elapse. Clearly, this has an important impact on the transfer timelines.

If changes appear unavoidable then an early dialogue with the regulatory authority is recommended, to ascertain whether upfront or concurrent stability is required. Provision of previous data coupled with MVTR data, product compatibility studies or

declarations from the container manufacturer of its suitability (conformance to FDA or DIN standards) for pharmaceutical use maybe sufficient to allow stability data to be produced post-commercialisation.

Another approach, if there are a number of different strengths of the same formulation, may be to use matrixing, i.e. provide data on the lowest and highest strength to negate the need for data on products in between.

For older products another complication maybe the stability conditions themselves. Older products may only have had stability data generated at room temperature (18-25°C) and ambient humidity. Upon transfer, stability data meeting ICH conditions will be expected, i.e. 25°C/60%RH. This may be too severe a challenge for either the formulation or the packaging system.

The latter may be correctable by increasing the barrier properties of the bottle or blister film (although not forgetting that this may have an economic impact) whilst the former may stop the transfer at worst, or require a reduction in the shelf life. Depending on the market competition, even this option may be unpalatable to the sales/marketing group.

4.8 Training

Regulatory agencies have been paying increasing attention to training of operational staff, as have most companies. It assumes even more importance during technology transfer for a variety of reasons.

Firstly, time constraints are normal and cutting training may be considered a soft option to save time. Secondly, the formulation, its manufacturing process, and the handling characteristics of the ingredients, may all be unfamiliar to operational staff. Thirdly the transfers will be under scrutiny, both inside and outside the operational unit, thereby increasing pressure on the staff.

Spending time on involving all relevant personnel in the process, providing appropriate and timely training, and encouraging staff to contribute to the process itself, will all help to minimise the likelihood of failure at what can be a stressful time for the organisation. It perhaps goes without saying that all training must be documented and increasingly "validated".

5 THE TECHNOLOGY TRANSFER REPORT

Regulatory inspectors and sometimes assessors will ask for evidence of successful transfer. This is more likely when the technology being transferred, be it the process or analytical method, is new to the site or poses particular challenges e.g. the introduction of bioassays. The report should also serve a similar function to the original development pharmaceutics report in that it provides a "ready reckoner" of

key aspects of the product and a reference point in the future if problems are encountered.

5.1 Contents

Generally the process consists of stages: (1) the generation of a protocol (a proposed structure for which is given below), and (2) a final technology transfer report, which includes all the raw data, or reference to where it can be found, together with a critical evaluation of the results.

Protocol Structure

(i) *Scope* - *a* clear statement of the product being transferred and what is involved in its transfer, i.e. process validation, analytical validation, cleaning validation, etc.

(ii) *Change management* - a statement of any changes being made as a result of the transfer, e.g. changes in source of actives, excipients, components, analytical methods and equipment, together with justification.

(iii) *References* - cross references to the original donor site documentation, e.g. manufacturing formulae, manufacturing methods, analytical methods, specifications for actives, excipients and components. Copies of these documents may usefully be attached to the report as appendices.

(iv) *Acceptance criteria* - a statement as to how the success of the transfer will be measured (see Section 4.5.1.5) for each of the processes involved.

(v) *Sampling regime* - a statement of the number, size and source of all samples and at what stage they will be taken.

(vi) *Recipient site documentation* - reference to any source documents used in determining the transfer approach, e.g. pharmaceutical development reports, analytical validation or process validation reports from the donor site.

(vii) *Additional requirements* - for example, if it has been determined that stability is needed then a copy of the protocol or reference to where the report may be found.

It may also be worth considering adding a section regarding the level of training considered necessary if the production, cleaning or analytical methods are complex or new to the site.

The completed protocol will be supplemented with all the raw data (or references to workbooks, data files, etc.) to form the final report and a clear critical evaluation of

the data and conclusion. If all acceptance criteria have not been met then a number of options need to be explored.

The transfer team, together with regulatory support, need to consider the nature of the failure and its impact on the robustness of the transfer. For example, if the cleaning validation fails, it can be considered that the manufacturing process is uncompromised, but a report addendum will have to be prepared clearly stating what corrective action has been taken and what results were achieved after implementation of the action.

Failure of the analytical validation clearly disrupts the programme as process validation cannot be initiated with a flawed analytical technique; or indeed any stability testing initiated.

Failure of the process validation is clearly very significant and it maybe very difficult to pinpoint what actions are required to correct the process. The normal causes of failure are inadequate distribution of the active and change in the dissolution profile.

Causes for the former may be inadequate mixing, over mixing (leading to demixing); disparate particle sizes of active and excipients; physical segregation caused by vacuum transfer systems; different bulk density leading to higher or lower loading in the granulator and subsequent changes in swept volume. For the latter, over mixing leading to "slicking" of the lubricant is a common source of failure.

Normally an extensive sampling regime is required to determine the root cause, taking samples potentially at every stage of the process. This additional testing should be defined by a new protocol which once more sets out the purpose of the additional work, the acceptance criteria, etc., and the work carried out. It may be helpful to include the corrective action report as an addendum to the original report. It may be wise to maintain an increased sampling regime following any corrective action, to provide additional confidence that the source of variability has indeed been identified.

It should be noted that the technology transfer report may be requested by the licensing authority in approving the site transfer, or by the inspectorate, as part of a pre-approval or normal GMP inspection.

5.2 **Approval Process**

The normal signatories of the technology transfer protocol are the team involved, regulatory affairs personnel, with a final approval to start from Quality Assurance. If the process involved is technically very complex it may be worthwhile, at the protocol initiation stage, to seek sign-off from experts at the donor site to ensure that (based on their better understanding of the process) all key criteria have been covered.

Once the work required to enact the protocol has been completed, and where timescales are very tight, it may be worth considering if commercial production can be effected against a review of the raw data, rather than waiting for the completion and sign-off on the finally completed report. This decision should be formalised prior to the transfer process being initiated not subsequently.

6 POST-TRANSFER EVALUATION

During the period of the transfer, close scrutiny of the process involved is maintained by the transfer team and hence it can be considered that the validations are somewhat "artificial". It is therefore worth considering putting in place a post-transfer evaluation process where say the first six or ten lots produced under standard production conditions are reviewed. Additional final product samples may be analysed and the results plotted using Shewarts charts or similar to establish process robustness.

Dissolution profiles rather than simply drug availability after a set time period may be considered. These results can be collated and added as an addendum to the original technology transfer report to provide powerful evidence of the success of the transfer validation. In those countries where Annual Product Reviews are mandated then any recently transferred product should be given priority review status.

7 TECHNOLOGY TRANSFER CHECKLIST

Below is a checklist that summarises the details that should be collated during the process, the majority of which have been referenced in previous sections.

Copy of Part 2 of Marketing Authorisation
Production Master Formula
Manufacturing Instructions
Dispensing Instructions
Analytical Methods
Previous Process Validation
Previous Analytical Validation
Cleaning Instructions/Previous Cleaning Validation
Stability Reports
Excipient Specifications and Source
Active Specifications and Source
Primary Packaging Material Specifications and Source
Packaging Instructions
Customer Complaints
Process Deviations File
Analytical Deviations File
Reject/Rework File
Specimen Manufacturing Batch Record
Specimen Cartons, Labels, Leaflets

SOURCES OF INFORMATION

Analytical Procedures Technology Transfer. ISPE Draft Guidelines. International Society of Pharmaceutical Engineers, ISPE European Office, 7 Avenue des Gaulois, 1040 Brussels, Belgium.

Cleaning Validation. Pharmaceutical Quality Group Monograph No. 10. Institute of Quality Assurance, 12 Grosvenor Crescent, London SW1X 7EE, UK.

Comments on the European Commission Guideline on Dossier Requirements for Type 1 Variations. MCA Eurodirect Publications.

Draft Guidelines for Validation of Analytical Procedures. International Committee for Harmonisation (ICH).

Guidance for Industry Changes to an Approved NDA or ANDA. Centre for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA).

Guidance for Industry SUPAC Manufacturing Equipment Addendum. Centre for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA).

Guidance for Industry Variations in Drug Products that may be included in a Single ANDA. Centre for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA).

Guideline on Dossier Requirements for Type 1 Variations. European Commission Enterprise Directorate-General.

Reviewer Guidance, Validation of Chromatographic Methods. Centre for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA).

EU documents are available on the website: **www.eudra.org**
FDA documents are available on the website: **www.fda.gov**

RELATED WEBSITES

The following websites contain more information and details of related titles:

www.dhibooks.com (Davis Horwood International Publishing Limited)

www.euromed-uk.com (Euromed Communications Limited) and also on the

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TECHNOLOGY TRANSFER IN PRACTICE

STEWART GREEN and PAUL WARREN
Wyeth Pharmaceuticals, Havant, UK

This concise overview of key points in the technology transfer process will be much appreciated in the current climate of mergers, takeovers and site transfer in the pharmaceutical and biotechnology industries. The purpose of this guide is to offer specific guidance on the key aspects, how such issues should be managed, how to document the outcomes to satisfy both internal and external regulators, and suggestions as to the personnel involved within the process. The guide offers a useful checklist as an *aide memoire* to ensure coverage of these key steps.

The principles discussed in the text can be applied in full or in part, dependent upon the nature and complexity of the product involved. Authors Stewart Green and Paul Warren offer many years "at the coalface" experience in this environment, and both are currently with the Quality Division of Wyeth Pharmaceuticals in Havant.

Topics covered include the technology transfer team, key activities such as timelines, regulatory issues, process scope determination, documentation, validation (including process, cleaning, analytical, validation, protocol; as well as packaging Issues, stability, reports, and post transfer evaluation. There is also a useful technology transfer checklist.

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