Supplementary Material

Table 1: Would an MCS assist you and why?

Increased knowledge and understanding

- The MCS would provide general minimum guidance updated using industry-wide information. Companies would have the option of building on this MCS framework to perform their own proprietary, more detailed risk analysis that would include a company's own knowledge, preferences, and expertise based on their own therapeutic areas.
- Provide a scientific rationale for selection of manufacturing process rather than an *ad hoc* approach.
- Promotes better understanding of the relationship between material properties and manufacturability. Should aid the harmonisation of what is considered to be important in terms of material physical/chemical attributes.
- If excipients are included, identify those that will most likely give a successful formulation.
- Identify the boundaries for material processing by using different approaches (e.g. DC, granulation).
- Stimulate research on linking properties from molecular to formulation level.

Streamlining pharmaceutical development

- A common understanding of risk would help in choosing a solid-dosage manufacturing process and would provide targets for API particle engineering efforts. This would allow formulators to learn from the experience of others avoiding time-consuming and costly trial-and-error approaches at the start of new development and deliver medicines to patients faster.
- The MCS would facilitate scale-up to clinical or commercial manufacturing facilities by providing a common language behind risk assessment ensuring that the chosen process is more robust by putting the process in the centre of the design space rather than at the edges. A more complex manufacturing process might have less worries about how the API will perform but more potential for troubles with scale-up.

Communicating formulation principles to non-formulators

- Selection of process technologies / manufacturing route for a new chemical entity should be

science-based but also a cross-functional decision. An MCS and, the visual interfaces embedded in such a tool (see examples in MCS paper), would help facilitate these internal discussions.

- MCS could help in evaluating dossiers for registration as it would provide common understanding for what is a low risk drug in manufacturing terms.
- When start-up companies bring a new API to a CRO for formulation, this will assist the CRO in explaining to their customer what is a realistic option.
- Aid in communication of the rationale behind drug product process decisions to non-formulators.
- Assist in setting expectations for API properties when sourcing alternative API suppliers.

It might be useful

- More defined criteria must be developed for ready adoption.
- As long it is not limiting or create a check box mentality.
- The MCS concept would be a great risk communication tool but I think there is too much weighting on API properties/risk and not enough on formulation properties/risk. To believe that API is mainly responsible for risk is not entirely true as both API and formulation/process can be modified to reduce quality risks. (Note formulation risk is also a function of dose).
- Need to ensure any MCS is actually comprehensive with very few "exceptions".
- This is an "expert system" approach and, as such, should be targeted at non-experts to give them broad guidance in the first instance and allow them to identify where detailed further studies are required.
- Need to fuse emerging simulation tools to manufacturing experience.

It would not be useful

- Already built into our formulation/process selection tools.
- Unique properties of API make classification very hard and limit creativity more than enabling more efficient techniques.
- The manufacturing process of (solid) dosage forms takes several steps. Will there be an MCS for each step? The overall process?
- Whilst it is good to discuss the relationship between material properties and manufacturing process, pigeonholing and rigid classification systems never delivered and cannot be substitute for a competent formulator.

- Will either be an over-simplification or too complicated.
- The major challenge I see to any guidance is accurately taking into account the variability that exist for each of the factors (batch variability, processing equipment output variability, environmental conditions variability) without defining ranges that are too broad to be useful.

Table 2: What next steps do you think the MCS working group should take?

Gather more data

- Collect data from companies on API properties, similar to PQRI Blend Uniformity survey [10]. Share data on percentage of process routes used in individual companies.
- Analyse existing API characteristics and their performance in different manufacturing technologies. Focus on properties which can be controlled through particle engineering.
- Develop modelling tools / small scale tests to measure properties and facilitate materials classification. Ensure these tests are agreed so that pre-competitive data is comparable.
- Determine whether these powder / bulk properties could be predicted from molecular properties.
- Establish a secure data platform to enable data to be collated and shared.
- The aim of data collection would be to determine how useful the MCS would be if it utilized a limited number of parameters.

Provide more detail on this initial skeleton

- Define the boundaries for DC, DG and WG and further develop the theory on percolation threshold.
- Determine how "close" a particular API is to being suitable for a particular category e.g. DC. If very close, may increase feasibility of particle engineering efforts.
- Develop the surrogate materials for each class. Prepare a monograph describing their properties.
- Define how other manufacturing technologies e.g. hot melt granulation, fit into the MCS. Also, is it possible to distinguish between the different types of wet granulation?
- Examine how the Other Technologies class links into the other 3.
- Give examples from real life wherever possible.
- Propose platform formulations based on each class.

Determine how continuous manufacture fits into the MCS

- What are the boundaries, i.e. when does poor flow become an issue for feeding.

Expand work on excipients

- An excipient can have very different compression properties depending on its quality. A spray dried version of e.g. mannitol (for direct compression) with optimized surface properties is more plastic than traditional qualities for e.g. wet granulation. We have tested optimized version of mannitol that has compactibility closer to MCC than would be expected.
- Consider collection similar data on excipients (powder properties, process intermediate properties, product properties).

Talk to other stakeholders for their input to MCS

- Early development as clinical trial material and processes selected for IMP manufacturing are also relevant.
- Excipient suppliers to better understand product properties that are governed by the excipient's functionality.
- Other profession bodies in the pharmaceutical sciences and chemical engineering professions e.g. AAPS, APV.
- Food industry with their extensive knowledge on processes.
- Academia for their experience with difficult compounds.
- Micronisation specialists.
- All of the manufacturers who supply instrumentation relating to the suggested measurements.
- Equipment manufacturers for the unit operations involved.
- Need to link this effort into other initiatives that are going on e.g ADDoPT.

Table 3: Reasons given in capsule filings for process choices

Drug	Company	Process	Justification
Cholic acid	Lucane	DEN	The finished product, powder-filled capsules, is a rather simple dosage form and no formal development studies were performed. Initially powder filled capsules with the active substance and lactose mix were made by the hospital pharmacy for the clinical investigations. This formulation was replaced by a to-be-marketed formulation, which is subject of this application. As there were no particular formulation issues with the active substance, a simple capsule formulation could be employed.
Dabrafenib	GSK	DEN	The objective was to formulate a simple blend that would be suitable for capsule filling using either gravity fed manual filling or a dosator type encapsulation machine.
Pregabalin	Mylan	DEN	Pregabalin is highly soluble over the physiological pH range and highly permeable (BCS I) and has reasonable flow properties. Therefore, a dry blending process was investigated, followed by filling into the hard capsules.
Pregabalin	Zentiva	DEN	Two different way of production were tested - wet granulation and direct mixing. Batch produced by wet granulation showed deterioration of impurity profile due to water, which contributes to Maillard reaction.
Indinavir	Merck	DG	A dry granulation method is used to avoid exposure to moisture, which has been shown to promote degradation to a lactone and aminoindanol. In view of indinavir sulphate's moisture and temperature sensitivity, poor flowability and relatively loose bulk density, a dry granulation formulation with acceptable compressibility and consistent fill volume during encapsulation was developed.
Stavudine	BMS	DG	Since the use of wet granulation resulted in hydrolytic degradation on storage at elevated temperatures, Zerit capsules are manufactured using standard excipients and a dry granulation process

Drug	Company	Process	Justification
			(slugging or roller-compaction) and then milling, followed by encapsulation.
Thalidomide	Celgene	DG	Roller compaction is employed to ensure consistent flow characteristics of the granulated powder blend during encapsulation.
Rivastigmine	Novartis	WG	In order to guarantee content uniformity at low strengths a wet granulation was the selected process.
Emtricitabine	Gilead	WG	A wet granulation process was developed and chosen over a direct blend in order to achieve the required density and flow properties for the powder blend to allow manufacture on an automated capsule filler.
Ribavirin	Teva	WG	Wet granulation was selected as the conventional method of converting powders into granules having a suitable flow and cohesive properties for both encapsulation and tabletting.
Sonidegib	Novartis	WG	The active substance has low density and poor flow properties and so a densification method was sought in order to produce a dosage form able to deliver the high doses required in early clinical studies. Direct compression and roller compaction methods were not suitable due to the poor flow properties and inherent low solubility of the active substance. Thus, a wet granulation process was investigated.
Atazanavir	BMS	WG	A wet granulation formulation has been chosen based on rapid and complete in-vitro dissolution profiles obtained. During granulation, the dissolution rate of the finished product is further improved by transformation of atazanavir sulphate crystalline form A into a predominantly amorphous form (see active substance). The amount of water for granulation being a critical parameter for complete conversion of the crystalline form, a suitable range of water has been selected based on X-ray diffraction pattern of development batches.
Anagrelide	Shire	WG	Wet granulation chosen in order to improve the dissolution performance and the content uniformity results.

Drug	Company	Process	Justification
Nilotinib	Novartis	WG	Considering the high amount of active substance per dosage unit and its physical characteristics (tendency to agglomeration and electrostatic behaviour, low bulk density), aqueous granulation was the method of choice.
Vismodegib	Roche	WG	High shear wet-granulation process produced granules with the best flow quality. Additionally, the granule particle size produced by high shear wet granulation was significantly smaller than that produced by the roller compaction process, which reduced capsule weight variation during encapsulation.
Atazanavir	Mylan	WG	Given the poor flow and solubility properties, a granulation approach was adopted.

Table 4: Reasons given in tablet filings for process choices

Drug	Company	Process	Justification
13-C Urea	Torbet Labs	DC	The active substance is hygroscopic and therefore precautions are taken to reduce humidity during the manufacturing process.
Hydroxycarbamide	Delpharm	DC	The poor compression properties of hydroxycarbamide (very poor cohesion properties, very bad capacity to transmit forces into the powder bed and hygroscopicity resulting in intense sticking during compression) have been compensated by a suitable choice of excipients. Silicified microcrystalline cellulose allows direct compression and sodium stearyl fumarate is used as a lubricant to decrease the level of friction, to improve the transmission of force into the powder bed and to decrease friability.
Lamivudine	Teva	DC	Ultimately, the direct compression process was chosen based on appearance and quality attributes of the product, as well as the simplicity and effectiveness of this process.
Levetiracetam	Ratiopharm	DC	Direct compression was selected for manufacturing the film-coated tablets since it is cheaper and demonstrated minor degradation of the active substance while processing.
Prucalopride	Janssen	DC	The wet granulation process was later replaced by direct compression due to the formation of a lactose adduct induced by exposure to moisture.
Sildenafil	Teva	DC	A direct compression with a non-micronised active substance was selected as manufacturing process because of the improved flow of the blend and the tablet compressibility.
Sitagliptin	Merck	DC	A direct compression manufacturing process was selected based on its inherent simplicity and demonstrated ability to produce high quality tablets reproducibly.

Drug	Company	Process	Justification
Trifluridine / tipiracil hydrochloride	Servier	DC	DC chosen to minimize exposure to the active during manufacture.
Olanzapine	Glenmark	DC	The drug substance is known to be sensitive to moisture. For this reason, a simple mixing direct compression process was selected.
Vardenafil Orodispersible	Bayer	DC	As rapid disintegration of orodispersible tablets based on Pharmaburst B2 is only achieved if addition of any binder is avoided, the powder blend is not granulated.
Emtricitabine / tenofovir alafenamide	Gilead	DG	FTC hydrolyses in aqueous solution.
Memantine	Mylan	DG	As a result of poor flowability and low assay values, a dry granulation roller compaction method was selected which gave acceptable content uniformity, hardness, and assay results.
Varenicline	Pfizer	DG	A dry granulation process was selected based on the improved process robustness gained by the resulting properties of the granulate, including improvements to flow and drug uniformity.
Axitinib	Pfizer	DG	The tablets used in early clinical trials were manufactured by a wet granulation process and were subsequently modified to dry granulation formulation to reduce processing time and material costs.
Colesevelam	Genzyme	DG	Dry granulation was employed to improve the flow properties and increase the compressibility characteristics of the granules.
Prasugrel	Lilly	DG	Due to prasugrel hydrochloride susceptibility to hydrolytic and oxidative degradation a dry manufacturing process was selected.

Drug	Company	Process	Justification
Vemurafenib	Roche	DG	The manufacturing process has been developed to comprise a dry granulation and thereby avoiding water in the process. By this, formation of crystalline Form II is avoided during manufacturing.
Canagliflozin / metformin hydrochloride	Janssen	WG	Fluid bed granulation was chosen over high shear granulation to meet the preferred wet granulation manufacturing platform due to the high drug load.
Emtricitabine / tenofovir disoproxil fumarate	Gilead	WG	A wet granulation has been chosen over a dry granulation in order to minimize the effect of the physico-chemical properties of the active substances on processing and blend uniformity. Control of the amount of unbound water during manufacture and in the finished product enhances to minimize any potential degradation.
Entecavir	BMS	WG	A wet granulation is used in the finished product manufacturing process, which minimises the impact of the physical characteristics (particle size, shape and surface area) of the active on the content uniformity of the tablets.
Lacosamide	UCB	WG	The properties of lacosamide suggested that a tablet manufacturing process based upon wet granulation might be suitable (high solubility and high permeability but low flowability).
Levetiracetam	Pharmathen	WG	Due to the high content of levetiracetam in the tablets the bulk has limited flow properties, thus wet granulation was chosen for the manufacturing process.
Oprymea	Pramipexole	WG	WG selected due to low dose.

Drug	Company	Process	Justification
Ribavirin	Teva	WG	Wet granulation was selected as the conventional method of converting powders into granules having a suitable flow and cohesive properties for both encapsulation and tabletting.
Sildendafil	Actavis	WG	A direct compression process was firstly tested. This approach was not successful due to the static nature of the drug. A wet granulation has then been chosen.
Sitagliptin / metformin hydrochloride	MSD	WG	A fluid bed granulation process was selected based on the poor compatibility of metformin hydrochloride and its high drug load in the fixed dose combination (FDC) tablet.
Tedizolid phosphate	Cubist	WG	A wet granulation process was selected in order to increase density and minimize the potential impact of drug substance content variability that can occur in early development.
Deferasirox	Novartis	WG	The physical characteristics of the drug substance resulting from micronisation (electrostatic tendency, poor flow and compression properties) have been compensated by a suitable choice of excipients and manufacturing process (aqueous granulation).
Dronedarone	Sanofi	WG	A wet granulation process was selected for the development of the tablet for industrial reasons, properties of dronedarone and because high dronedarone strengths were requested.
Fosamprenavir	GSK / Viiv	WG	Due to a combination of high drug content and small particle size of the drug substance causing poor blend flow properties, direct compression was not feasible and a classical high shear wet granulation process has been developed.
Irbesartan / Hydrochlorothiazide	Teva	WG	Due to the high percentage of the active substances in the formulation, wet granulation process was selected.

Drug	Company	Process	Justification
Ketoconazole	HRA	WG	Due to the high content of the active substance in the tablet formula (about 65%), wet granulation was selected for the manufacture of the tablets.
Raltegravir / Lamivudine	MSD	DG / WG	Because of the known stability of raltegravir in fluid bed granulation processes, a high shear wet granulation procedure was investigated in order to improve scalability, increase relative raltegravir composition in the tablet and afford suitable mechanical properties. A high relative drug loading was required in tablets order to meet the QTPP, but lamivudine exhibits poor flow properties for formulation. Therefore, a roller compaction process was developed in order to improve flow properties and allow for granules with high drug content.
Nevirapine	Boehringer Ingelheim	WG	The standard wet granulation process was selected since it provided good flow characteristics and ease of manufacture.
Olanzapine	Mylan	WG	A wet granulation process was considered the most appropriate in order to avoid segregation during manufacturing. Nevertheless, direct compression process was attempted, but the results confirmed that wet granulation was the best option.
Pioglitazone	Krka	WG	During the formulation development both direct compression and wet granulation were compared and wet granulation selected since it was found to give better physical properties.
Rufinamide	Eisai	WG	At the very early stages of development, uncoated tablets of 1 and 10 mg were produced by direct compression. However, as the dose had to be increased, direct compression was impossible due to the poor flow characteristics of rufinamide. Higher strength (50 and 100 mg) uncoated tablets were developed using the dry “roller” compaction method, but flowability problems were observed during the dry compaction process. As a further increase of the dosage strength to 400 mg was necessary,

Drug	Company	Process	Justification
			further changes in the composition and in the manufacturing process of the product were made in order to achieve an acceptable weight and size of the 400 mg tablets and to overcome the technical problems observed in the roller compaction process. A wet granulation method was introduced.
Tadalafil	Mylan	WG	As the active substance exhibits poor flow properties, a wet granulation process was selected for prototype formulation development.
Telmisartan	Actavis	WG	The manufacturing process selected was fluid bed granulation in order to improve the flow properties of the raw materials and to increase the solubility of the active substance.
Vandetanib	AZ	WG	Conventional wet granulation approach was selected as vandetanib has sub-optimal compression properties and is incorporated into the tablets in a high load.
Vorapaxar	MSD	WG	The direct compression manufacturing process was changed early to a wet granulation process upon content uniformity considerations (2.08mg dose).

Table 5: Description of Other Technologies used in capsule formulations

Drug	Company	Description	Reason for OT
Mercaptamine	Raptor	API is dissolved to form a wet blend with the excipients (to generate an extrudate.	Development of an enteric coated dosage form.
Linaclotide	Almirall	Gelatin capsules filled with linaclotide-coated microcrystalline cellulose beads.	Low dose, API incompatibilities with excipients.
Dimethyl fumarate	Biogen	2 mm enteric-coated microtablets in size 0 hard gelatin capsules.	The aim was to develop a delayed-release formulation that prevents release of the active ingredient in the gastric environment while allowing for rapid release of the active ingredient in the intestine region.
Enzalutamide	Astellas	Solubilised drug in a soft gelatin capsule	Bioavailability was greater when enzalutamide was dosed as a solution rather than as a suspension or solid formulation.
Nintedanib	B.I.	Soft gelatin capsule containing suspension of the API.	The selection of formulation was based on the relative high drug load, the properties of the active substance and excipient compatibility results and also to minimize the exposure of manufacturing personnel to the active. Due to poor solubility of the API at neutral conditions, it cannot be formulated as solution and is therefore suspended in a lipophilic fill mix. Milled active substance is used to prevent generation of active substance agglomerates in the fill mix.
Tipranavir	B.I.	A self-emulsifying drug delivery system (SEDDS) in	Overcome the dissolution rate limited absorption of the tipranavir drug substance, since the drug is dissolved in the SEDDS vehicle.

Drug	Company	Description	Reason for OT
		a soft gelatin capsule.	
Dabigatran	B.I.	Active ingredient layered organic acid containing pellets filled into hard capsules.	Other formulation approaches evaluated during early development, were inferior to the selected formulation in terms of drug load, stability and *in vivo* performance. The active substance is susceptible to hydrolysis in presence of humidity under acidic conditions, which is why a manufacturing process limiting water and acidic conditions is chosen.
Aprepitant	Merck	Coated microcrystalline cellulose beads.	Active substance particle size milled to nanoscale in order to enhance the bioavailability. Formulated to ensure particle remain small and re-disperse *in vivo* to nano-size.
Tafamidis	Pfizer	Suspension in soft gelatin capsule.	Active gelled during disso from conventional hard gelatin formulation. A suspension formulation was required as tafamidis showed poor solubility in many of the vehicles commonly used in formulating soft gelatin capsules
Fenofibrate / pravastatin	SMB Tech	Fatty semi-solid composition consisting of 160mg fenofibrate and (B) a coated tablet containing 40mg of pravastatin sodium	Increasing solubility using an amphiphilic excipient in order to enhance its bioavailability.

Table 6: Description of Other Technologies used in tablet formulations

Compound	Company	OT Description	Reason for OT
Asenapine	Organon	Freeze dried dispersible tablet	Initial development examined a conventional oral solid dosage form, however, low bioavailability (<2%) caused by extensive first-pass metabolism dictated that another route be adopted, and it was decided to follow the sublingual route. The experience of the finished product manufacturer was utilized in the development of sublingual tablets, through a freeze-dried matrix of gelatin and mannitol.
Clopidogrel hydrochloride	KRKA	Melt granulation	A thermoplastic based granulation has been selected as manufacturing process especially in view of safety and environmental issues and it provides good reproducibility and scale-up.
Cobicistat	Gilead	Deposition on silicon dioxide	Form considerations (ref [1])
Oestrogens conjugated / bazedoxifene	Pfizer	Active coating	Duavive is a modified release film-coated tablet, designed to provide an immediate release of BZA in combination with a controlled release of CE.
Olanzapine	Lilly	Freeze dried	Dispersible tablet
Repaglinide	Novo Nordisk	Spray dried granules	Gives optimum distribution of the active substance in the matrix of the tablet.
Saxagliptin	AZ	Active coating	Saxagliptin is prone to undergo an intra-molecular cyclisation reaction in solution and solid states to form a cyclic amidine. The active coating process to minimizes this formation.
Telmisartan	Bayer	Spray dried	No reason given.

Compound	Company	OT Description	Reason for OT
		granules	
Vildagliptin / metformin hydrochloride	Novartis	Melt granulation	No reason given.
Sirolimus	Pfizer	Active coating	In order to improve the stability and bioavailability of the coated tablet, the active substance was incorporated in a NanoCrystal Colloidal Dispersion in which the drug particle size is reduced to nanometer dimensions in the presence of a stabiliser (poloxamer 188). The Nanodispersion containing sirolimus and the stabiliser is added to a sugar coating suspension, used to coat inert tablet cores previously overcoated with shellac and inert filler coats. The last coat is the colour coat.