EFPIA-EBE White Paper on Expedited CMC Development: Accelerated Access for Medicines of Unmet Medical Need – CMC Challenges and Opportunities (Final Version - December 2017)

It should be noted that the opinions shared in this document are the opinions of the EFPIA/EBE Trade Associations and should not be construed as defining any regulatory positions of the EMA. It is stressed that companies are urged to seek appropriate advice from competent authorities for specific application of any CMC expedited approaches.

Executive Summary

Since 2012 there has been a focus on faster translation of scientific breakthroughs to new, high quality medicines meeting unmet medical need through a programme initially referred to as Medicines Adaptive Pathways to Patients (MAPPs). In response to this in 2016 EMA introduced two new regulatory approaches; namely Adaptive Pathways (AP) and Priority Medicines (PRIME). At present, there is limited mention of CMC aspects for those accelerated access approaches in the public domain and this EFPIA-EBE White Paper seeks to outline options for the acceleration of CMC development that may be acceptable to Regulatory Authorities for medicines exhibiting the potential to meet an unmet medical need without compromising their quality or safety.

Underlying principles and illustrative examples of CMC approaches to development and manufacturing which a company may undertake to facilitate accelerated review or early access are described. A number of important regulatory considerations are also outlined and some initial considerations to support accelerated and novel approaches to CMC development are presented. Those suggestions must be viewed on a case by case basis and are in no way construed to represent a guarantee of accelerated review or early access. It is strongly suggested that sponsor companies wishing to adopt these approaches engage with the EMA through Scientific Advice as early as possible and that the Agencies reciprocate by enabling timely access to, and involvement of, the necessary technical experts to promote those discussions.

Consideration is given to the challenges posed by the accelerated development of both small molecules and large biopharmaceuticals. Detailed suggestions and a comparative assessment contrasting with conventional development activities are presented in two additional annexes with the aim of promoting further industry / regulatory collaborative development.

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Introduction

In June 2012 the European Federation of Pharmaceutical Industries and Associations (EFPIA) Board adopted the R&D and Regulatory Pathways Strategy with the objective of adapting the regulatory and development models to scientific progress and rationalizing them to improve R&D productivity and probability of success. A key component of this strategy was the Medicines Adaptive Pathways to Patients (MAPPs) initiative, which was aligned with the EMA Adaptive Pathways (AP) project.

MAPPs referred to an overall framework which described proposals for addressing all aspects of adaptive approaches from early development to patient access and for the life-cycle of the therapy. It aimed at faster translation of scientific breakthroughs to new, high quality medicines benefitting patients and society, improving dialogue between industry, patients, regulators, Health Technology Assessment (HTA) bodies and payers during the development process. Its ultimate aim was to reduce uncertainty for innovators and increase predictability for patients.

In 2016 the PRIME (PRIority MEdicines) scheme became available in Europe, for registration of selected medicines, to enhance support for the development of medicines that target an unmet medical need. The scheme is based on enhanced interaction and early dialogue with developers of highly promising medicines, to optimise and ensure robust development plans and speed up evaluation and initial approval so these medicines can reach patients earlier.

Problem Statement

An accelerated clinical development programme will usually be a prerequisite for acceptance onto an accelerated access scheme project. This will decrease the amount of time available for the development and understanding of the drug substance, the drug product and their associated processes; therefore, there must be a strategy to ensure that the critical aspects of Chemistry, Manufacturing and Controls (CMC) provide assurance that safety and quality will not be compromised. This strategy must also assure the flexibility needed to deliver consistent and reliable supplies of product to patients in a less predictable environment, with potential controlled distribution to patients.

Situation

At present, there is limited mention of CMC aspects for accelerated access approaches in the public domain even though there is a need to expedite CMC aspects to keep pace with any accelerated clinical programmes. This White Paper has therefore been developed as part of the accelerated access initiatives, and seeks to outline options for the acceleration of CMC development that may be acceptable to Regulatory Authorities for medicines exhibiting the potential to meet an unmet medical need without compromising their quality or safety.

Illustrative examples of CMC approaches to development and manufacturing which a company may undertake to facilitate accelerated review or early access are described. A number of important regulatory considerations are also outlined and some initial considerations to support accelerated and novel approaches to CMC development are presented. While general concepts are provided here, it is understood that the application of those suggestions to a development programme must be viewed on a case by case / product basis and are in no way construed to represent a guarantee of accelerated review or early access. It is strongly suggested that sponsor companies wishing to adopt these approaches engage with the EMA through Scientific Advice as early as possible and that the Agencies reciprocate by enabling timely access to, and involvement of, the necessary technical experts to promote those discussions.

An initial discussion took place in January 2015 between representatives of the former EFPIA Technical Development and Operations Committee (TDOC) and the EMA Quality Working Party (QWP) and Biologics Working Party (BWP) on critical technical and regulatory aspects. A follow up discussion was held in February 2017 between members of the EFPIA Technical Development Expert Group (TDEG), EMA, QWP and BWP in relation to the first draft of the paper. This revised version of the White Paper is intended to provide more details on proposals for further industry / regulatory collaborative development.

EFPIA-EBE Guiding Principles and Assumptions

In considering how the challenge of expediting the CMC development of new medicines can be met, EFPIA and EBE believe that a number of principles need to be agreed and applied that will facilitate the science- and risk-based assessment of new approaches:

- An expedited CMC approach must always ensure product quality and patient safety whilst enabling the earliest access possible for patients;
- Both small molecule and biologic products are deemed to be in scope (including drug-device combination products, ATMPs, and oligonucleotides);
- Both drug substance and drug product are in scope; The aim must be to minimise the areas of uncertainty;
- Regulator(s) will enter into early discussion with the sponsor to agree on a viable expedited development programme;
- Consideration of an expedited CMC approach is comprised of three essential elements:
    I. aspects associated with commercializing a new product more typical of a late stage Investigational Medicinal Product than Commercial Product;
    II. commitment, timescale and assessment of an ongoing rolling submission of data, if required;
    III. potential adoption of new working practices, predictive models and technologies that reduce uncertainty, provide greater verification and may help offset some of the traditional CMC data required at the time of filing in (ii);
- During the period of the rolling submission where the reviewer and inspector are both closely involved, the Competent Authority should provide the sponsor with integrated assessments.

CMC Challenges and Considerations

In order for CMC not to be on the critical path for early access, adaptations to the traditional approach to development and manufacturing may be required. This can be exemplified by further expanding on elements (i) - (ii) mentioned above:

- **(i) Aspects associated with commercialising a new product more typical of a late stage Investigational Medicinal Product than a Commercial Product**
    - More focus on testing, verification and concurrent validation;
    - Commensurate with the conditions and controls used for the manufacture of late stage clinical trial materials;
    - Possibly launching from an R&D pilot plant facility;
    - Maybe limited in manufacturing flexibility;
    - May utilise controlled distribution or other alternative distribution models to allow a shorter shelf life to be used initially;
    - May leverage knowledge that the manufacturer has from similar products and processes to accelerate decisions and support proposals for manufacture and control;
    - Increase leverage of knowledge of risk-based approaches based on the Biopharmaceutical Classification System.

- **(ii) Commitment, timescale and assessment of an ongoing rolling submission of data, if required**

  Early access may often entail a reduced level of CMC information at submission and include a plan for making additional information available during review, before launch or at a later defined time point. As a consequence, the CMC data/documentation package will most likely need to evolve over the lifecycle of the product.

  For example:

  - Provisional acceptance criteria in specifications upgraded to final acceptance criteria;
  - Provision of long-term stability data at a later stage, including the possibility of providing during the review cycle (where it is not possible to use data from stability modeling – refer to ASAP section in Annex 2);
  - Provision of stability data from Commercial scale at a later stage;
  - Scale-up activities and/or transfer to a Commercial site;
  - Control strategy evolving over time;
  - Alternative approaches to process validation.

A number of CMC approaches to development and manufacturing which a company may take to enable early access are provided in more detail in Annex 1.

Regulatory Considerations

As stated by the EMA, the AP approach is based on a prospectively planned (regulatory) process starting with the early identification of programs with the potential to be progressed under AP, followed by supportive engagement of regulators/HTAs with the sponsor, leading to a marketing authorisation (MA) of the medicine in the EU, in a restricted patient population. In some cases a full MA may be granted from the beginning. The EMA emphasize that the AP initiative builds upon regulatory processes already in place within the existing EU legal and regulatory framework

In the case of PRIME, the scheme equally builds on the existing regulatory framework and tools already available such as scientific advice and accelerated assessment. This means that developers of a medicine that are accepted into PRIME work closely together with EMA towards being eligible for an accelerated assessment at the time of application for a marketing authorisation.

EFPIA and EBE agree and wish to provide comments on aspects of the existing EU regulatory framework that can usefully be considered for development in support of those accelerated access approaches. For example, the current procedure for CHMP Scientific Advice, as well as the existing MA mechanism may warrant some consideration for further flexibility to support expedited initiatives and, in addition, may also lead to some considerations related to post-approval change management.

We detail some of these aspects further below:

CHMP Scientific Advice Process

The current CHMP Scientific Advice framework is considered useful to sponsors, but might not be flexible or responsive enough to provide the extensive and continued dialogue between sponsor and competent authorities that will be essential for successful support of pharmaceutical development, review and post-approval activities for products licensed through an accelerated access scheme. It is acknowledged that through those schemes there is the opportunity for more informal interaction between a sponsor and the Agency. Also, EFPIA and EBE are aware of ongoing EMA consideration of

improvements to its Scientific Advice processes and interactions with companies. EFPIA and EBE welcome such initiatives to improve the Scientific Advice process and to augment this in support of the accelerated access initiative. A more flexible and responsive advice procedure for qualifying candidates will be of great value, and could encompass, e.g. more numerous, less formal interactions between sponsor and EMA working parties/ committees outside of formal Scientific Advice. The appointment of a 'pharmaceutical development rapporteur', and even early appointment of the rapporteur for the MAA assessment would facilitate such communication and allow for understanding and continuity of the program agreements made during development into the MAA review process and beyond, similar to the assignment of an early rapporteur in the new PRIME scheme. This increased and highly supportive exchange on an individual project would then form the basis to agree with the agency CMC aspects that could be deferred post-submission or post-approval whilst providing a development approach, manufacturing process and control strategy which provides for patient safety and supports accelerated patient access. It is important to also ensure that flexible access to any previous scientific advice gained is taken into account by the Rapporteur and a process for CMC modality experts to be brought into the advice process to be considered.

In addition, there may also be significant value in engaging the inspectorate function in such advisory discussions with the sponsor of an expedited program to support planning for the most effective and efficient provision of the product to patients upon approval under the expedited initiative.

Marketing Authorisation Process (and the link to post-approval optimisation of the product)
The existing MA mechanisms may similarly benefit from some further adaption to the potential outcomes of the development of a product under an expedited initiative, where a somewhat different or limited CMC package may be provided at the time of initial MAA submission. Useful adaptations may include providing possibilities of reviewing certain CMC information when it becomes available ("rolling" review) or proceeding with a review without certain CMC information (e.g. confirmatory stability data, site specific batch manufacturing data, process validation/verification data etc.) on the basis of alternative approaches to the development of the product.

There may also be the possibility of "uncoupling" the clinical/ non-clinical and CMC submission packages and reviews, and, very importantly, fully enabling post-approval substitutions to the dossier as per agreements reached.

A consequence of conducting an accelerated development may very likely be a need for an increased number of changes (including supplementation of additional data) to be made in the period following initial approval, compared to a traditional development. It is important that this factor is carefully analysed and several approaches considered balancing this change in paradigm. For example, it will be very important to develop mechanisms to understand how changes can be made to such products approved under an expedited initiative without adding significant time to the implementation of change. An approach that might need to be considered is how the pre-submission advice to the sponsor under the expedited development paradigm can be embedded in the ongoing lifecycle management of the product, for example by means of pre-discussed and agreed commitments associated with the approval, e.g. as follow-up measures.

There is an already existing regulatory tool, the post-approval change management protocol (PACMP), which may be used for situations where completing some activities prior to the initial submission (e.g. change to site of manufacture or scale) is not possible or a certain sequence of development events cannot be altered. The PACMP is well suited to define proactively and agree with the competent authorities how significant or more complex changes may be handled post-

approval and how the information in the regulatory dossier will be supplemented, and managed during an inspection. Thus it can serve as an enabler in supporting change management in accelerated CMC projects. Whilst not every CMC aspect in an expedited development program will need to be managed by a PACMP (or other appropriate follow-up measures) it may even be the case that several PACMPs, or one PACMP including multiple changes if appropriate, are associated with an expedited MAA submission. In such circumstances, a comprehensive overview of all PACMPs in the dossier would be useful for the reviewer and could be part of an overall lifecycle strategy document, as currently discussed in the context of the ICH Q12 guideline.

Global considerations

The topic of accelerated development and approval pathways for medicinal products of high unmet medical need has gained significant global attention over the last few years. Given that similar CMC challenges can be anticipated in all regions involved (e.g. in the US through the Breakthrough Therapy Designation initiative and in Japan through the Sakigake Pathway), EFPIA and EBE would like to highlight the importance of global convergence of major regulatory agencies in terms of CMC expectations and provision/ use of regulatory tools in support of these new pathways. Such international alignment would facilitate global expedited development and best support rapid patient access to new, important therapies across the world.

Accelerated and Novel Approaches to CMC Development and Association with IMI-2 ADAPT-SMART

Although the primary aim of accelerated access schemes is to examine how to expedite the current approaches to medicines development, access and regulatory oversight, there is also an opportunity for expedited development to act as both a stimulus and accelerant to the creation and approval of alternative paradigms and technologies for more efficient development and manufacture of drug substance and drug product, whether they be small molecule or biologic in nature.

Developments in biotransformation, process analytics, *in-vitro* modeling, scale independent production and advanced packaging offer significant opportunities in drug substance and drug product development to shorten the overall time from bench to market access without any reduction in the oversight of consistent, reliable and stable quality. This can be illustrated by expanding on item (iii) from the section on EFPIA-EBE Guiding Principles and Assumptions.

- **(iii) Potential adoption of new working practices, predictive models & technologies that reduce uncertainty, provide greater verification and may help offset some of the traditional data commitments required in (ii)**
    - Simplification through reduced complexity of formulation and unit operations;
    - Control strategies that begin to move away from reliance on sampling to 100% verification;
    - Greater utilisation of predictive modelling to reduce uncertainties and perform more targeted experiments
        - Impurity purging
        - Scale-up effects
        - Accelerated stability and modelling of degradation
        - Meaningful application of mean kinetic temperature
        - PK profiling;
    - Selection of more protective packaging
        - E.g. vacuum packaging to guarantee stability over a longer period.

The success of the application of accelerated and novel approaches to CMC development will require a collaborative effort that is fully supported by an equally progressive regulatory strategy from competent authorities. To this end the EFPIA TDEG MAPPs sub-team has linked with the IMI-2 ADAPT-SMART programme and specifically the CMC aspects of “Evidence Generation through the Lifecycle”. This has entailed a mapping study of data sources, tools & methodologies relevant to biopharmaceutical development/CMC data generation in the context of expedited development and the creation of a gap analysis based on this evidence.
For illustrative purposes, the following six CMC areas have initially been identified as potential opportunities for delivering reduced pharmaceutical development times, and are expanded in separate sections in Annex 2:

1. Biopharmaceutics
    a. Computer Based Models
2. Formulation and Manufacturing Process
    a. Use of *In-Silico* Tools
    b. Continuous Manufacturing
    c. Use of Modelling to Facilitate Scale-Up and Verification
3. Process Validation
4. Stability/Shelf life

    a. Accelerated Stability Assessment Protocol (ASAP) Studies
5. Control strategy
    a. Impurity Fate Mapping – Purge Modelling
6. Further Considerations for Biotech Products
    a. Process Validation
    b. Use of Prior Knowledge: Viral Clearance/Inactivation Steps
    c. Manufacturing Changes to Support Commercialisation.

Conclusions

EFPIA and EBE fully support the overall aims of the EMA accelerated access approaches to enable a more timely access for patients to new treatments that significantly improve their quality of life. In order to achieve this goal, we believe that modifications to the traditional CMC development paradigm will need to be supported, as well as the introduction of an appropriate level of dialogue between the MAH and the Competent Authority (incl. modality SMEs) to facilitate the initial approval as well as a more effective life-cycle management of CMC documentation associated with a product submitted through an accelerated access programme.

Version 1.0 of this document was shared with EMA in February 2016 and version 2.0 in May 2017. In publishing version 3.0 of this document in January 2018, it is the intention to update this document on the basis of further discussions with appropriate stakeholders and as new information becomes available.

Annex 1: Illustrative Examples of Adaptations of Traditional CMC Development and Manufacturing Approaches for Drug Substances and Drug Products to Enable Accelerated Access

The following table illustrates some approaches which a company may take to facilitate early access of medicines.

N.B. this table is not intended to be comprehensive. Most aspects of the proposals are valid for small molecules/ NCEs as well as large molecules/ biotech products.

Topic	Traditional approach	Accelerated Access aligned approach
Formulation	Commercial formulation developed and optimised; comparability to pivotal clinical formulation demonstrated in dossier.	Use of clinical formulation, or limited optimisation of selected market form. Where relevant, comparability of launch formulation to pivotal clinical formulation demonstrated in dossier. Where relevant/known, planned commercial formulation described and a PACM Protocol to demonstrate comparability to pivotal clinical formulation in the dossier.
Presentation (drug/device combination)	Optimised for patient population, required usability studies completed	Clinically appropriate; improved patient convenience presentation (e.g. vial to pre-filled syringe or auto injector) in development. Usability studies with representative labeling ongoing, complete data before launch
Packaging	Optimised, based on minimum requirements for protection.	Potential for initial use of “maximum protection pack” to mitigate limited shelf-life.
Labeling	Labels in all languages and pack based information driven by national requirements.	Initial launch (where agreed) of multi-language packs to ensure rapid availability of important products as soon as possible after approval across the EU.
Analytical procedures	Developed and validated.	Developed and qualified; validated, with potential scope for exemptions.
Specification	Established and documented. Supported by extensive dataset.	Established and documented; possibly broader specifications as little data is available. May include some parameters where the data will be reported but acceptance criteria not defined. Commitment to update (rationalise) after x time or y batches, based on pre-defined criteria and to reassess the control strategy.
Impurity assessment	Impurities identified, risk assessed and controlled.	Impurities identified, risk assessed and controlled. Higher level of control by specification testing (could include intermediates) may be needed until sufficient data available to support greater reliance on process control.
Shelf-life	Shelf-life at launch based upon defined length of stability data on defined batch types/sizes (ICH Q1A). Limited extrapolation. Post-approval extension as	Launch product will be supported by (ongoing) stability studies, but ICH conform data may be limited. Reliance on lean stability strategies (including stress conditions), use of stability models, and extrapolation for supporting shelf-life, enhanced use of scientifically relevant supporting data from earlier batches, and possibly more data to be

Topic	Traditional approach	Accelerated Access aligned approach
	further data emerges.	made available in ongoing stability. Post-approval strategies will depend on formulation strategy and may also involve novel approaches.
Process development	Complete package at filing. Process supported by extensive development studies	Partly based on platform knowledge, to be refined as more batches/materials are investigated. Process accepted on normal operating ranges based on limited stretching.
Process validation	Prospective or Continued Process Verification.	Concurrent validation approach, including extended monitoring.
Scale of production	Commercial scale	Small commercial or IMP scale. Scale-up protocol defined.
Sites of production	Commercial manufacturing site. Existing cGMP clearance or Inspection–ready. Multiple sites may be included.	May be clinical manufacturing site. Existing cGMP certificate (possibly only MIA-IMP). Inspection–ready; product history available to support approval of clinical site for commercial launch. Site addition PACM protocol defined.
Sales and Distribution	National level wholesale and direct to institution supply chain sales.	Potential for changing scale over time From: IMP scale individual patient shipments direct to physician pan EU with the addition of reimbursement: To: Full scale traditional commercial scale sales and supply.
Viral Clearance Validation	Validated in small scale.	If appropriate platform data are available: include such data in dossier, validate in small scale prior to launch, and agree mechanism for provision of data to Competent Authorities.
Inspection of facility	GMP certificate available for commercial use of the facility.	Acceptance of GMP certificate for IMP manufacture or, where facilities are outside the EU, the acceptance of QP Declaration for imported API/product, if not assessed by Inspection by a Member State.
Cleaning method	Established	Established
Cleaning validation	Validated	Appropriate verification through analyses on batch-wise basis
DMFs (where used)	Submitted in close conjunction with MAA	Negotiate early submission/pre-assessment to mitigate risk of landing on critical review path.

Annex 2 - Accelerated and Novel Approaches to CMC Development

Biopharmaceutics

Computer Based Models (small molecules)
In an expedited development paradigm, early investment in developing a deep understanding of fundamental biopharmaceutical properties of the active substance and product can reduce the overall time to develop a robust high quality drug product with the desired clinical performance, and reduce uncertainty around subsequent formulation and process optimisation steps and product establishment at the commercial site.

Utilising a combination of advanced bio-relevant *in-vitro* systems and *in-silico* Physiologically Based Pharmacokinetic (PBPK) models, in combination with agile and information-rich clinical study designs, will enable rapid development of drug products with optimal performance. Advanced *in-vitro* dissolution models such as the TNO-TIM1 can be used to predict *in vivo* dissolution and streamline selection of API solid form and formulation platforms. Advanced *in-silico* PBPK models can be used to reduce uncertainty around likely clinical performance and inform formulation selection and Phase 1 study design. Investing in formulation understanding studies earlier in development will streamline later development and formulation bridging approaches, and build confidence in the *in-vitro* and *in-silico* models. The use of flexible adaptive designs for clinical formulation performance studies can facilitate rapid formulation selection and development by enabling teams to respond to the data from each study cohort to inform the design of the next; additionally the use of the IV micro-tracer technique (where a concomitant intravenous radio-labeled micro-dose is given with an oral dose) enables generation of intravenous PK data much earlier in development, which significantly reduces the uncertainty around *in- silico* pharmacokinetic predictions. The IMI OrBiTo project will deliver further advances in *in-vitro, in-vivo and in-silico* biopharmaceutics tools.

There is an opportunity to move beyond traditional BCS thinking to understand *in-vitro/in- vivo* relationship on a product-specific basis, using the tools described above to enable the establishment of clinically relevant *in-vitro* tests and acceptance criteria. This, in combination with *in-silico* modeling, can be used to facilitate rapid process establishment, optimisation and scale up based on knowledge of the potential *in-vivo* impact of any changes, and ultimately define the control strategy to ensure that drug product of suitable clinical quality is always delivered.

Formulation and Manufacturing Process

Novel approaches to formulation and process design: Use of *in-silico* tools (small molecules)
Over the last 10 years there has been considerable development in computer simulation of pharmaceutical materials, processes and product performance, enhanced by the significant advances in computational performance and measurement technology. Increasingly, mechanistically based models provide a sound basis for describing 'prior knowledge' of the behaviour of the systems being described. The increase in available models provides an unprecedented opportunity to apply a systems-based approach to formulation and process design linked to pharmaceutical product quality and performance. The applications of this modeling paradigm present opportunities for product design (model based optimisation to meet desired product specifications), process optimisation, identification of design space, control strategy identification and risk assessment and sensitivity analysis.

Specifically, in an expedited development paradigm, *in-silico* tools can be utilised for formulation and process selection with the associated mechanistic understanding of *in-vitro* and *in-vivo* performance, including the impact of product stability. In many cases these models can be built or calibrated using specific experimental measurements of physical properties or one to a few carefully designed experiments, rather than relying on a purely empirical understanding driven by extensive experimental design methodologies. This can facilitate rapid development, with data generation being specifically targeted to build models or validate formulation and process prototypes. It is important to recognise that the prior knowledge that comes with utilisation of increasingly mechanistic *in-silico* models allows greater product and process understanding to be obtained from experimental calibration and validation, rather than experimental mapping or interpolation. This will also lead to enhanced process establishment with reduced experimental packages, speeding up clinical supply and ultimately commercial supply. Furthermore, the impact of unseen future changes (for example, raw materials) can be anticipated and explored using *in-silico* models, thereby improving future process capability and security of supply for patients.

The following are key initiatives in this area:

- Digital Design (iUK funded project – 2014 start for 2 years) – provides a modelling framework for global sensitivity analysis of pharmaceutical processes and product performance;
- Digital Design (AMSCI project – 2015 finalising agreement) – improving model fidelity and multi-scale modeling from molecule to product performance.

Continuous Manufacturing (small molecules and large molecules)
Traditional batch processes for the manufacture of both drug substance and drug product are being complemented by the use of continuous processing methods. The use of continuous processes allows innovative methods of drug substance manufacture to be used (for example, the use of highly selective reactions or otherwise hazardous materials). Due to the nature of the equipment it is possible to rapidly develop the manufacturing process, for example, to optimise reaction conditions and to assess critical manufacturing parameters. The use of 'self optimising reactions' is also an exciting opportunity that is currently being developed between industry and academia. Once developed, the scale up of continuous processes is, to some extent, easier to predict than for batch processes therefore the quality of material produced at laboratory scale is likely to be indicative of the quality produced at commercial scale manufacture. It also offers benefits for supply chain for products where the predicted volumes of drug substance and drug product are uncertain i.e. it is easier to stop and start continuous processes than batch processes. This methodology is also amenable to innovative analytical methods such as in-line process monitoring which can be used for continuous process verification.

Use of Modelling to Facilitate Scale-up and Verification (small molecules and large molecules)
Scale-up Verification using process modelling techniques (for example multivariate analysis (MVA) or chemical reaction kinetics) can positively impact CMC development, in terms of delivering enhanced process understanding and accelerated scale-up and development.

For drug substance and product processes designed at small scale, verification that they scale-up as predicted to intermediate and commercial scale can be achieved more rapidly and with greater confidence through the application of scientific principles, e.g. process kinetics and process modeling techniques such as MVA. This obviates the need for additional experiments at intermediate and commercial scale. The approach is aligned and supports plans to commercialize from pilot-scale facilities. It provides enhanced process understanding more rapidly than traditional

qualification/verification approaches, giving confidence in predictions of how processes will run at larger scale.

Process Validation (small molecules)
In an accelerated development programme, the period of time to gain extensive product and process knowledge before commercial manufacture will be significantly shortened. The extent to which a process may be run at commercial scale may be limited and much of the process knowledge will be derived from small scale experiments, platform knowledge or *in-silico* modeling. This places increased emphasis on the process validation activities. The use of development and establishment batches as part of a more holistic process validation activity is one of the ways to accelerate this phase of the product lifecycle. In addition, there must be acknowledgement of the need for increased use of concurrent validation to ensure that production specifically for a process validation is not necessary.

Given the potential for limited process knowledge, acknowledgment by regulatory authorities that changes may occur during establishment and validation activities is critical, as long as these changes are critically evaluated for impact to product and other produced material.

Data from early campaigns can be used to support validation when a detailed and robust monitoring and sampling plan should be initiated as early as possible during development. Even after completion of process validation, it is likely that there will be limited amounts of process data available. Therefore, the use of an enhanced monitoring period during commercial manufacture may be required. This will facilitate ongoing statistical analysis and trending of batches, providing data on the capability and stability of the process and product and facilitate process enhancements post-approval.

Stability/Shelf Life
Accelerated Stability Assessment Protocol (ASAP) Studies (small molecules and large molecules)
Accelerated stability studies utilising modelling for predictive stability assessments have the potential to play a key role in the expedited development and delivery of accelerated access projects. Accelerated Stability studies employ an iso-conversion paradigm, and a humidity-corrected Arrhenius equation to provide reliable estimates for temperature and relative humidity effects on degradation rates. These experimental data when combined with an appropriate statistical protocol gives an opportunity for the prediction of chemical stability, which in turn allows for an accurate estimation of shelf life.

ASAP studies give a greater insight into the stability of a product than traditional stability studies where the focus is on demonstrating stability rather than understanding it. By thoroughly understanding the stability of a drug product or drug substance, data driven decisions can be made throughout the development process and ensuring that the process can be expedited at every opportunity.

By utilising ASAP studies, it is possible to rapidly assess the impact of changes to a process, mitigating the risk of making such changes and ultimately demonstrating the stability after the change. If the registration stability batches are no longer fully representative following a change to the process, ASAP data can be used without the requirement to produce additional formal stability studies before regulatory submission. This is particularly of interest when development timelines are restricted and the time for additional stability studies to be completed would significantly delay the marketing of the product.

ASAP studies also allow an estimation of the impact of humidity on degradation of solid dosage forms, and can be combined with Moisture Vapour Transmission Rate (MVTR) of the packaging and moisture sorption isotherms of the internal components to identify the most appropriate packaging configuration for the solid oral dosage form. Moreover, any changes to the configuration i.e. change in tablet count, desiccant, wall thickness, initial moisture content can be accurately predicted without the need to repeat the stability studies.

Where there is a need to assign a shelf life or retest period within a restricted timescale in order to expedite regulatory submission and delivery of medicines to patients, it is possible for ASAP studies to be used as the primary source of stability data to predict and assign these shelf lives and retest periods, utilising limited long term 'traditional' stability data as supportive data to verify the model over a shorter timeframe. This would significantly reduce the time for development, and where necessary the long term stability data can be provided post approval to demonstrate the appropriateness of the stability assignment. This strategy has already been utilised for post approval changes.

Control Strategy

Impurity Fate Mapping - Purge Modelling (small molecules)

The ICH Guideline M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, advocates the use of *in-silico* structure-activity modeling to identify potential mutagenic impurities. M7 then allows for multiple approaches for the control of mutagenic impurities, including analytical testing, chemistry purge arguments or a combination of the two.

Many impurities are highly reactive, will not typically survive through the synthetic processes and therefore present negligible risk of carry over into the drug substance. Despite this, completion of spiking and purging experiments which demonstrate the purge of low levels of mutagenic impurities can be a time limiting element in drug substance development, particularly the development and validation of the sensitive analytical procedures required.

Teasdale *et al* published on a purge concept that is working towards a common industry framework and tool for assessing the purge of an impurity based on readily calculated physic-chemical factors. This approach allows for the development of a systematic *in-silico* approach for quantification of the risk of impurities remaining in a drug substance. Software under development will allow a user to enter their synthetic route, highlight the impurities of concern and estimate the purge values for them at each stage. Such software tracks the impurities from introduction through to the drug substance and the calculated purge factors can be used to support scientific arguments *in lieu* of analytical testing (Option 4 of the Control of Process Related Impurities section, ICH M7 guideline). Ongoing optimisation of this software is driving the creation and development of a reactivity database of purge values which will significantly enhance knowledge of the fate of all impurities in chemical reactions. The scope of the *in-silico* purge tool therefore goes beyond ICH M7 and will enable faster decisions during development and minimise the need for resource intensive fate and effects studies to understand impurity purging.

Further Considerations for Biotech Products:

Process Validation

For all biotechnological products there is a need to provide results of process verification studies on production scale batches in the MA dossier at the initial filing. As these process evaluation studies are often on the critical path, it might delay the submission of the dossier and, as a consequence, could result in delayed access of products of unmet medical need to patients.

It is therefore proposed for accelerated development programs (via an accelerated access scheme) to allow for the absence of process validation data in S.2.5 and P3.5 at the time of submission if

mitigated by inclusion of an appropriate protocol describing the process verification program and ongoing/continued process verification studies. Like for small molecules, the actual results of the process verification studies need to be made available for verification post authorisation by the supervisory authority.

Use of Prior Knowledge: Viral Clearance / Inactivation Steps
(Adopted from EBE Concept Paper on Platform Manufacturing of Biopharmaceuticals).
The viral clearance steps in a mammalian cell-derived biopharmaceutical manufacturing process are almost always considered when the use of platform process data/ knowledge is discussed. This is due to the fact that typically the same virus clearance studies are executed multiple times under the same protocol on different protein molecules. The different proteins, especially those from the same 'family' of molecules, e.g. monoclonal antibodies, generally show similar behavior at the different clearance steps (filtration/ low pH or chemical inactivation/ chromatography) which are operated the same way (platform process) for each product. These repeated studies tend to yield consistent and similar results from product to product.

Published data from a large drug manufacturer's development and marketed product portfolio show the inactivation of murine leukemia virus (MuLV) through low-pH treatment of suspensions of numerous different monoclonal antibodies. After experimentally executing low-pH inactivations for sixteen different IgG molecules, the step has been proven capable of achieving the minimum acceptable log reduction values (LRV) under a variety of conditions. The data indicate there is little or no incremental value in executing a further pH inactivation study on another IgG protein in the pipeline - further data will only verify what is already proven. Indeed, the recent *CHMP Guideline on Virus Safety Evaluation of Biotechnological Investigational Medicinal Products* (2008) acknowledges that prior in-house experience and data may be used to support the reduction in virus clearance testing for investigational products under clinical development.

EFPIA / EBE believe there is an opportunity to eliminate such repetitive internal testing of well-characterized viral clearance steps and save time in an accelerated development scenario.

In addition, numerous other published studies have demonstrated the capability of established downstream process steps for viral clearance. For example, the clearance of the simian virus type 40 (SV40) at an ion exchange step using Q-Sepharose Fast Flow (QSFF) resin and under different operating conditions was consistently > 5 log10 for a number of monoclonal antibody preparations from a company (see: Curtis, S. et al. (2003) Generic/Matrix Evaluation of SV40 Clearance by Anion Exchange Chromatography in Flow-Through Mode, *Biotechnol. Bioeng.*, 84, 2, p.179).

The data in this and other publications are a useful reference to support the principle of generic or modular viral clearance steps, but usually a drug manufacturer must develop its own in-house data to support its case that a clearance step can be applied to new products.
EFPIA / EBE support the possibility to reference to peer-reviewed published viral clearance studies (such as the example cited above) in an accelerated development project for a given viral reduction step/claim without repeating the same studies again in-house, and gaining agreement to this approach early in the development.

Manufacturing Changes to support Commercialisation
Under an accelerated access scheme it may not be feasible to perform pivotal clinical studies with the "to be marketed commercial process" thus necessitating further changes to the process that will be reflected by updating/ supplementing the initial MAA. The assessment of the changes and the supportive data to ensure the safety and efficacy of the changed process will be completed in a step-

wise manner as would be done with other "non-accelerated" products (i.e. estimate product risk level, categorize type of CMC change, evaluate outcome of *in-vitro*/*ex-vivo* characterization and assess – if applicable - need/ type of *in-vivo* testing). In expedited schemes, where appropriate and justified, the use of prior knowledge/ platform knowledge will be leveraged for the comparability assessment. Three potential manufacturing changes are briefly discussed below with proposed supportive data packages. This is not an exhaustive list.

Cell line

A change of cell line is common during the development of a biotech product to ensure sufficient and robust commercial supply. However, it is considered a major change and is normally implemented as early as possible during development (prior to pivotal studies). It is therefore proposed that such cell line change may be performed during or post pivotal studies to enable early licensure under the accelerated access scheme for cases where there is convincing comparability evidence. In such a scenario, a comprehensive analytical comparability package would be required, ensuring that each potentially impacted CQA has been assessed. It may also be pertinent to include the use of established animal models in PK/ PD studies to support the analytical comparability where appropriate.

Process scale-up / Change of Site of Manufacture

A change of the process scale and/ or site of manufacture is usually considered a major CMC change. Within an accelerated clinical programme, it may not be possible to perform the technical transfer into the commercial facilities and/ or manufacture at full scale for pivotal clinical studies. We consider it acceptable that manufacture for pivotal studies and initial launch could be performed at a smaller scale or a clinical manufacturing site (provided both adhere to cGMP), with analytical comparability data being presented at their earliest availability to support the switch to the commercial manufacturing site post launch. Process validation would then be provided post-approval based on data created at the commercial site.

Manufacturing Process Development Data / Control Strategy

For accelerated development, where appropriate and justified, the sponsor will leverage platform or prior knowledge for the marketing authorization application under the expedited scheme. Further, the process control strategy will be refined and confirmed as more batches/ materials are manufactured. The initial manufacturing process may be based on preliminary ranges and specification acceptance criteria that might be broader than for products developed in a traditional setting and will be reassessed when a more comprehensive data set is available.