
Annual Industry Report

Industry Expert Panel Submissions



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On Target with Antibody Drug Conjugates

Summary of market predictions

- Pharma and biotech to invest more heavily in the ADCs market based on the targeted delivery action and hence reduced side effects of cancer treatment by 2020
 - A blockbuster drug likely for treatment of solid tumours in next 10 years
- Majority of ADCs in the next 5-years will be for Lymphoma indication
- ADCs market to be worth \$10 billion by 2023
- IND submissions expected to rise by 50% over the next five years based on the recent trend in the R&D pipelines of innovator companies
- The biggest hurdles in the ADC field which include conjugation technologies and linker chemistries are slowly being overcome with the entry of more companies with their own conjugation technologies and linker chemistries
- Also the hurdle of a complex supply chain in terms of the manufacture of the mAb, the linker, the cytotoxic/highly potent molecule and then the conjugation is now being overcome with more companies offering more than one portion of this supply chain

"In the past a major failing with ADCs has been that cytotoxic agents were simply not active enough to kill the target cell with such a small amount of payload - 0.01% - however new technologies that improve antibody and antigen conjugation could hold the key to really unlocking their potential. Over the next 10 years we will see ADCs with higher penetration rates, and even products designed for indications beyond cancer – like inflammation"

Vijay Shah

Introduction

With the recent approvals of Adcetris (brentuximab vedotin) and Kadcyla (ado-trastuzumab emtansine), antibody drug conjugates (ADCs) represent a growing area in oncology with great potential. With the success of Kadcyla against solid tumours comes the real promise of ADCs in tackling the most aggressive and resistant tumours with the worst clinical outcomes. Current targets include difficult-to-treat cancers such as triple-negative breast cancer, gastric tumours, small-cell lung cancer, melanoma and pancreatic cancer. More than 30 other ADC candidates are currently

in trials for about 25 different targets, with many more programs in development. The number of ADC candidates in the clinic has doubled since 2010, and further growth is anticipated.

Now that the therapeutic potential of the class is finally being realised, ADCs have become a hot field in research and development, with most major pharmaceutical companies either already established in the area or looking to get involved. Many collaborative deals have been

announced, including the recent deal between Pfizer and CytomX, worth a potential \$635M.

The rapid growth in ADC technology is being driven by the flexibility of the platform. Conjugation is applicable to all antibody technology types, including full-length

monoclonals, antibody fragments and bispecifics. Both antibodies and cytotoxics that have previously failed in the clinic can even be given a new lease of life as ADCs. In addition, their potential is not just limited to oncology – they are also being investigated for indications such as inflammation.

Market Potential

The long term future of ADC programs is difficult to predict, but their potential to extend the on-patent life of existing products and maintain market position is attractive to pharma companies. Kadcyla is a good example – it extends the potential of Herceptin as the monoclonal antibody itself approaches the end of its patent protection. New ADC products like Kadcyla, with their increased complexity, will offer oncology companies new ways to discourage biosimilar competition in the future.

Most analysts predict that ADCs will become a major product grouping within the oncology market, but the main obstacle to widespread uptake is their extremely high price – Kadcyla costs more than twice as much as Herceptin, and both the currently available ADC products are priced at around \$100,000 per patient treatment regimen. Although Kadcyla does show patient benefits over the current best treatment option – extending median life expectancy by six months while reducing serious adverse events by about a third – at a time of squeezed health budgets, achieving high patient uptake is likely to be challenging. Nonetheless, analysts are predicting a market size anywhere between \$2 billion and \$5 billion for Kadcyla, compared to the total annual sales of \$6 billion for Herceptin. It is likely to be the largest ADC product for the foreseeable future, on account of the large existing market for Herceptin.

The majority of the ADCs that are set to reach the market in the next few years are for lymphoma indication. They are likely to be treatment options for smaller patient groups,

and there is greater opportunity for competition. The sales figures for Adcetris thus far give a greater insight into the potential future sales performance of ADCs. It targets a much smaller patient population than Kadcyla, but the benefits are much more significant. However, the very high per-patient cost has led to slower uptake than had been predicted, and it has failed to live up to market expectations. Recent quarterly sales of \$34.5 million, Jan-Mar 2012, were somewhat short of the anticipated \$39 million. Regardless, Adcetris is still predicted to be a big seller, and sales of \$1 billion a year might even be achieved. The main driver for this growth is an expanding pool of patients who might benefit from the drug, in the light of ongoing clinical trials that are investigating earlier use, and its potential in a wider range of cancers.

The full potential of the ADC market will become clearer in the next few years, as additional products progress through late-stage clinical trials. ADCs are expected to make up more than 10% of revenues for the total antibody market, approximately \$10 billion by the end of 2023, according to a recent market analysis report from ADC Review: Journal of Antibody Drug Conjugates. The number of IND submissions for ADC products is accelerating – more than 30 from 2008 to mid-2012, compared to 15 between 1993 and 2007. The attrition rate remains relatively low and, given the current pipeline, multiple ADC products might be expected to reach the market by 2020. Key programmes to watch will be those in difficult-to-treat solid tumours, and success here would likely generate multi-billion dollar drugs.

Targeted Therapies

The success of these ADC therapies comes from a combination of a highly potent toxin with the ability of a monoclonal antibody to target malignant cells. The benefit of targeted delivery of therapeutics was predicted long before it was possible to achieve. Early experience in the oncology field demonstrated the benefit of chemotherapy in treating metastatic disease, but the lack of specificity of the treatment severely limits therapeutic success. Greater discrimination between malignant and healthy tissue is required but, to date, this was difficult as the therapies used were, essentially, non-targeted.

The innate specificity of antibodies was recognised early on and, in combination with the identification of tumour-specific antigens, this opened the door to the possibility that tumour cells might be selectively targeted and destroyed. The concept is simple, but the results obtained were, at first, disappointing. Big advances were required for the industrial production of antibodies, and to overcome the first wave of setbacks from issues such as immunogenicity. However, the success rate remained low with the first monoclonal antibody therapies, especially in solid tumours. There was huge excitement surrounding these early targeted antibody therapies in cancer, and there were a few notable successes. But it did not transform the outlook for patients which, in all too many cases, remained poor.

The lack of success of monoclonal antibodies in cancer treatment did not result from lack of specificity, but more from a lack of activity. They could be shown to reach and bind to receptors on the tumour cells, but they did not seem to recruit the immune system to destroy the tumour as had been anticipated. In most cases, the antibody had little or no effect, and the treatments only showed significant value as a component of a multi-agent chemotherapy regime. Outcomes improved a little, but side-effects still limited treatment because of the non-specific activity of the other components of the chemotherapy regimen.

The components required for a potential 'magic bullet' therapy were now coming together. Advances in chemotherapy, radiotherapy and monoclonal antibodies

sparked a further round of enthusiasm, as many groups looked at combining cytotoxic chemotherapy agents with monoclonal antibodies. Two main approaches were attempted. First, existing chemotherapy agents such as anthracyclins and vinca alkaloids, with known clinical benefits, were conjugated to monoclonal antibodies. The second looked to direct radioisotopes to the tumour via the conjugation of radioisotopes, or chelating groups that bind them, directly to the antibody.

As before, the early optimism faded as the first antibody conjugates hit the clinic. Although exciting data had been seen in preclinical models, all too often the results in patients did not meet expectations. Some even showed a lower clinical efficacy than the untargeted cytotoxic. Radioisotope conjugation showed some success but, again, the results were far from the breakthrough that had been hoped for. Early successes were limited to haematological cancers, with solid tumours proving remarkably resistant. Three programmes had some success in the clinic: one antibody drug conjugate (Mylotarg – gentuzumab ozogamicin) and two radioconjugates (Bexxar – tositumomab and iodine 1131 tositumomab, and Zevalin – ibritumomab tiuxetan conjugated with yttrium 90). Mylotarg's ozogamicin payload had never been used as an unconjugated cytotoxic because of its extremely high potency. The drug was voluntarily withdrawn from the market in 2010 after little evidence of clinical benefit in the acute myeloid leukaemia it was licensed to treat.

Significant side-effects were also seen with all three of these products as, despite the targeting activity of the antibody, off-target damage was still occurring at dose-limiting levels. Mylotarg has serious liver toxicity, while the radioimmunoconjugates irradiate healthy tissue around the cancers – and elsewhere in body as they circulate in the bloodstream. The beta and gamma emitting isotopes travel far from the point of origin, leading to wide-ranging irradiation of healthy tissue.

Research into the early failed conjugates determined that access to the tumour was a significant factor limiting the therapeutic effect. A study suggested that only about 0.01% of the conjugate actually reached the tumour and was

internalised. This explains the failure of the early conjugates using existing chemotherapy agents; the cytotoxic agents were simply not active enough to kill the target cell with such a small amount of payload entering the cell.

Improving drug properties

The early experience with ADCs quickly confirmed that the technology was going to be significantly more complicated than first expected. Further progress would need to be made in antibody selection, the payload and the linking chemistry to join the two elements together. Target selection would also be key for a successful conjugate. A suitable antigen target would be significantly overexpressed on a cancer cell compared to healthy cells. It also has to be expressed on the cell surface at points that are accessible to the antibody. For an ADC, the antigen needs to be internalised, although this is not a requirement for a radioimmunoconjugate. Not many antigens meet these criteria, and this is a key area for research.

One antigen that does meet these requirements is HER2. It is substantially overexpressed on many breast cancers to a level significantly higher than healthy tissue. It is internalised on binding by an antibody and trafficked to the lysosome for degradation allowing payload release. Experience with Herceptin (trastuzumab), which targets HER2, highlights the potential of this antigen as a target for ADCs.

The choice of antibody has to complement the antigen. All antibodies against an antigen are not equal, and some will have much more preferable characteristics as therapeutic agents. The binding affinity, epitope bound on the antigen and the antibody class all have an impact on the suitability of the antibody for use as an ADC. Currently IgG1, IgG2 and IgG4 isotypes are used, as well as antibody fragments and antibody fusion proteins. There are advantages for each approach. Full-length monoclonal antibodies are still the most common. They have long circulating half-lives, and can retain full antibody functionality, which may enhance potency. The size of the fully intact antibody may count against it, however, when it comes to penetrating into a solid tumour. Small molecules are more likely to enter the tumour, which may favour smaller antibody fragments. However, this must be balanced against renal clearance, which will shorten circulating half life dramatically. Bifunctional and other engineered antibodies potentially offer greater functionality and specificity. The science behind selecting the best antibody is still in its early days, but this is an active area of research, and is sure to become better understood as more successful ADCs are identified.

Linker choices

The linker is an important element of the ADC, and its importance was underestimated in the early products. Initially, most researchers assumed the linker would have to be cleavable to release the active free drug. The challenge thus became finding a linker that could be cleaved inside the cancer cell, but was stable in the circulation to prevent the highly potent drug from being released in the circulation. Three main approaches came from the lysosome, which would be the final destination of the ADC. First, the endosome has lower pH, and acid labile linkers could be useful. Hydrazone chemistry was used as this is relatively stable at physiological pH, but unstable at the lower pH of the endosome. Secondly, the lysosome

has proteases such as cathepsins, which could digest peptide linkers. Peptide linkers that contain a target cut sequence for cathepsins were tested. Finally, the lysosome was thought to be a reducing in nature, so disulfide bond-containing linkers were investigated. A variety of cleavable linkers was identified that exhibited good stability and activity.

Surprisingly, non-cleavable linkers also showed promise, as they were active for some drugs when the full antibody was digested, liberating the cysteine / lysine conjugate of the drug linker that retained activity. Both cleavable and non-cleavable drug linkers are active in cancer cells, but show

considerable differences in efficacy. This is often specific to the individual cancer cell line. One observation was that cleavable drug linkers could release an active free drug that killed the target cancer cells, but also antigen negative cells nearby. This effect was termed bystander killing, and while it is useful for tumours with heterogeneous target antigen expression, it comes at the cost of more off-target toxicity. Non-cleavable drug linkers tend to generate free drug with a charged lysine or cysteine amino acid attached. This prevents passive uptake into neighbouring cells, and prevents bystander and other off-target toxicity.

The linker can also provide other benefits. For some drugs, aggregation is a big problem. Many highly

potent drugs used in ADCs are very hydrophobic and, consequently, can promote denaturation of the antibody during conjugation. Early products used un-optimised linkers that did little to space the drug the optimal distance away from the antibody, or introduce a more polar structure to the overall drug linker to add solubility. Recent developments have used linkers based on polyethylene glycol and other biologically compatible polymers to improve solubility and drug loading. Increasing the polarity of the drug linker also has a secondary effect, in that it may make the drug linker less of a suitable substrate for multidrug resistant proteins that pump the toxins out of the cell. This is now a key area of research.

Forming the links

In terms of the linker chemistry, two main conjugation routes have been used. Most antibodies have no free cysteine groups, but these can be generated by the partial reduction of inter-chain disulfide bonds. This provides reactive thiol groups that are easy to conjugate using a variety of different chemistries. This method creates pairs of free thiols, as each disulfide bond is reduced. Different combinations of disulfide bonds are reduced in the reaction, and a variety of different species is created. For an IgG1, conjugates containing 0, 2, 4, 6 or 8 highly potent drug molecules are produced, and the average drug load is adjusted by titrating the molar ratio of reducing agent to the antibody. The resulting conjugate is stable despite the reduction and conjugation of the interchain disulphide bonds, but stability remains a concern after these key structural groups have been broken. Traditionally, maleimides have been reacted with the thiol groups. Exchange reactions have been reported with other thiols, but these may result in off-target toxicity.

The second route is via reaction with lysine residues on the antibody. In this process, the antibody's disulfide structure is retained, but it can alter the overall charge of the antibody, depending on the chemistry used. The main issue with lysine chemistry is the large number (>25 for IgG1) of conjugatable lysine residues within the constant and variable regions of the antibody. For most antibodies with

an average load of 3 to 4, there will be species ranging from 0 to 8 drug loading, with the drugs distributed between any of the conjugatable lysines. As a result, the product may be very heterogeneous product, posing a huge analytical challenge.

For both cysteine- and lysine-linked conjugates, it is likely that higher loaded species, while more potent, are more likely to be cleared from the circulation and cause off-target toxicity. Unconjugated antibodies may act as a competitive inhibitor, while conjugates with a low loading may not be sufficiently potent. Both cysteine- and lysine-linked conjugates have recently been commercialised, proving that either system can result in successful ADCs.

The drawbacks associated with the traditional chemistries have resulted in major research programmes looking at site-specific conjugation chemistries, and improved chemical conjugation techniques. Groups researching improved chemical conjugation techniques are developing chemistries that are more robust than those using maleimides, and which are capable of re-bridging the disulfide bond after conjugation. This can also generate more controlled drug-to-antibody ratios, and give a maximum drug load of 4 for an IgG1. This type of technology has an advantage that the antibody does not need to be reengineered.

However, other site-specific technologies do require the antibody to be engineered. The first approach was to engineer additional cysteines into the antibody. As with many aspects of ADC development, this looked to be a simple approach, with the introduction of a specific residue for conjugation, but it proved much more difficult than anticipated. The engineered cysteine residues were found to be capped, and very little free thiol was present. While the free thiols could be regenerated by reduction, a selective re-oxidation step was necessary to re-form the disulfide bonds while leaving the engineered thiols free for conjugation. Although this is possible, it requires the engineered cysteine

groups to be carefully positioned in the antibody to prevent crosslinking and disulfide scrambling. A different approach involves using engineered cell lines to insert non-standard amino acids into the antibody. These can provide the basis for more specific conjugation chemistries, such as copper-free click chemistry. Peptide sequences recognised by particular enzymes can also be used for enzymatic conjugations. A wide range of site-specific conjugations is being developed, and it is likely that this will become the next standard. Site-specific conjugates are now in clinical trials, and the first successful site-specific conjugate will likely set a new standard for the development of conjugates.

Toxin selection

The final element is the choice of toxin. The relative success of Mylotarg over other early ADC conjugates demonstrated the requirement for a highly potent payload. Microtubule disrupting drugs (vinca alkaloids) and DNA damaging compounds (anthracyclins) were first developed as payloads for ADC use, but lacked potency. Screening for novel cancer agents had identified many very highly potent cytotoxics, but most of these had failed to progress clinically as a result of their very narrow therapeutic window for these compounds. Dolastatins and maytansinoids had been identified as highly potent microtubule disrupting agents, but failed in Phase I trials as unconjugated drugs because of their dose-limiting toxicity. However, they are currently the leading payloads in ADC therapy, with Adcetris using the

dolastatin derivative auristatin E, and Kadcyra using the maytansine derivative DM1. The calicheamicin payload used by Mylotarg is still in use following improvements to the linker chemistry, and the anti-CD22 ADC inotuzumab ozogamicin is currently in Phase III trials.

Despite this success, new payloads are required, especially those with new mechanisms of action. Other payloads under development include the DNA-damaging duocarmycins and pyrrolbenzodiazapenes, which look to be more potent than the microtubule disrupting drugs, with greater activity against slowly dividing cancer cells. Other novel payloads include the highly potent amatin RNA polymerase II inhibitors derivatives isolated from the death cap mushroom.

Manufacturing challenges

The development and manufacture of ADCs can be a challenge, as it requires the ability to handle both biologics and highly potent small molecule toxins. This combination of capabilities is not often found in the same organisation, and only a relatively small number of CMOs cover the ADC manufacturing space. As the clinical trial results of ADCs continue to be largely positive, with few failures, this will put a strain on ADC manufacturing capacity. In-house manufacture will be difficult for many pharma companies,

particularly those with a small number of programs, and experienced ADC CMO capacity is limited.

ADCs offer the potential to revolutionise cancer treatment. After many false starts, the potential of this technology is now becoming clear. The true potential of this technology may be realised in coming years, when it will become evident whether the success of the recent commercialised products can be repeated, especially in the treatment of solid tumours.



PANEL MEMBER

Dilip Shah, CEO, Vision Consulting Group

Drug Regulatory Scrutiny & the Pharmaceutical Industry

Summary of Market Predictions

- The pharmaceutical industry is facing increased scrutiny by regulatory authorities globally, and in particular the FDA, which is establishing progressively higher standards of safety and quality
- Both big pharma and small companies are still failing in terms of cGMP compliance, and the number of drug recalls, market withdrawals and safety alerts reported over the last three years indicates that while many instances of noncompliance are inadvertent, some are deliberate
- As analytical technologies improve it is likely that the number of violations detected will increase further
- Increasingly stringent requirements and regulatory authority vigilance will prevent some smaller companies from entering the US market, ultimately reducing competition over coming years
- Industry must effect a cultural change in attitude, and implement processes both vertically and horizontally, enterprise wide, to keep up with a changing regulatory landscape and meet requirements
- Some collaboration and cooperation among drug regulatory authorities will help to cut development costs and reduce duplication, but large-scale integration of the global regulatory landscape is unlikely to be comprehensive over the next five years
- While the responsibility for willfully contravening regulations, for example by selling unapproved drugs,

must lie solely with the industry, the regulator should take some responsibility for issues such as inadvertent cGMP deviations, and help advise and guide the industry to ensure it can meet manufacturing and drug quality and safety standards

- The regulator will need to become more transparent, and effect dialogue with the industry to teach, encourage and monitor best practice, and help address issues as its requirements become ever more exacting

The pharmaceutical industry is facing increased scrutiny by drug regulatory authorities across the world. Perhaps most notable of these is the US FDA, which requires the highest standards of drug safety and quality, and which employs rigorous investigative techniques and skills that are formidable from the perspective of any company. The adoption of progressively higher standards of safety and quality has led to a greater focus on data integrity and cGMP compliance, but the pharmaceutical industry's lack of awareness and inadequate appreciation of these continually evolving standards has resulted in many companies failing to meet requirements. Given that the US is the single largest market for medicines and its regulatory authority is considered a benchmark, this article focuses on FDA data as the foundation for analysis, and suggests action plans for improving compliance.

How Many, and For What?

An analysis of warning letters issued over the last 42-month period (January 2010 to June 2013) by the Office of Manufacturing and

Product Quality provides some useful insights into the changing profile of regulatory inspection and oversight.

Table 1

Warning Letters by Office of Manufacturing & Product Quality, US FDA

No	Issue	2010	2011	2012	2013*	Total
A Active Pharmaceutical Ingredients (APIs)						
1	Mfg facility inspection	2	8	5	1	16
2	Deviations from cGMP	5				5
3	Change notification	-	1			1
Total APIs		7	9	5	1	22
B Finished Pharmaceuticals (Formulations)						
1	Mfg facility inspection	2				2
2	Violations of cGMP	5	10	16	12 ^(a)	43
Total Formulations		7	10	16	12	45
Total API + Formulations		14	19	21	13	67

Source: www.fda.gov

(a) Includes API Mfg Facility Inspection of one Unit

* To 30 June Only

Table 1 shows that during the last 3.5 years warning letters relating to APIs, which largely concern manufacturing facility inspection, have decreased, whereas those relating to formulations have increased. It is evident from these figures that the detection of cGMP violations at formulation units is growing alarmingly. A further analysis of this data shows that 66 companies received a warning letter during the 42-month period, with one company, Apotex, receiving two. Prominent names among those on the receiving end of warning letters highlight both innovators and generics

companies, including Boehringer Ingelheim, Hospira, Merck KGaA, Novartis, Novo Nordisk, Sanofi Aventis, SmithKline Beecham, Teva and Wyeth Lederle. Indian companies, which account for 40% of DMFs to date and 37% of ANDAs in 2012, accounted for 12% of the warning letters.

A similar analysis of warning letters issued by the Office of Drug Security, Integrity and Recalls during the same period (Table 2) provides another useful insight, and suggests that internet marketing is still eluding regulatory oversight.

Table 2

Warning Letters by Office of Drug Security, Integrity & Recalls, US FDA

No	Issue	2010	2011	2012	2013*	Total
1	Internet Marketing of Unapproved and Misbranded Drugs	-	2	6	-	8

Source: www.fda.gov

* Up to 30 June Only

The study also examined Drug Recalls, Market Withdrawals & Safety Alerts during the 42-month period, as shown in Table 3.

Table 3

Drug Recalls, Market Withdrawals & Safety Alerts by Reason, US FDA

No	Reason/Problem	2010	2011	2012	2013*	Total	% of Total
1	Undeclared ingredient; including sildenafil, acetaminophen, dexamethasone, diclofenac, etc.	17	14	8	9	48	27.0
2	Visible particulates; including fungal microbial contaminants, precipitation/crystallization, brass particulates, etc.	0	12	15	11	38	21.3
3	Unapproved drugs	1	2	7	4	14	7.9
4	Sterility	0	0	4	10	14	7.9
5	Deviations in fill volume, Size/Thickness of Tabs, variations in tablet strength, etc.	0	3	7	1	11	6.2
6	Packaging error; including mislabeled/incorrectly labeled bottles, and bottles containing wrong drugs, etc.	0	6	3	1	10	5.6
7	Quality control and manufacturing processes, insufficiencies in the development of the manufacturing process or non-compliance with drug manufacturing requirements	1	1	0	1	3	1.7
8	Equipment cleaning, leading to product containing trace amounts of other drugs	0	1	0	1	2	1.1
9	Others; including contamination, odour, impurity, leaking container, difficulty in using measure dosing system, etc.	0	18	13	7	38	21.3
Total		19	57	57	45	178	100.0

Source: www.fda.gov

* Up to 30 June 2013

Further analysis of Drug Recalls, Market Withdrawals & Safety Alerts, by company, is presented in Table 4 below:

Table 4

Drug Recalls, Market Withdrawals & Safety Alerts by Company, US FDA

No	Frequency	2010	2011	2012	2013*	Total	% of Total
1	1 Time	17	24	30	25	96	80
2	2 Times	1	4	3	6	14	12
3	3 Times		2	1	1	4	3
4	4 Times	1		1		2	2
5	5 Times		1			1	1
6	> 5 Times		2	1		3	2
Total		19	33	36	32	120	100

Not Learning from Mistakes

The 178 incidents reported in Table 3 relate to 120 companies. Ninety six of these were the subject of just one drug recall, market withdrawal or safety alert but, as shown in Table 4, another 24 companies were caught out more than once, and five of them more than five times. These include American Regent (13 instances), Hospira (10) and Bedford (6). Three major Indian companies, Glenmark, Sun and Ranbaxy, were among those companies that each had one violation.

The number of firms named through FDA drug recalls, withdrawals, or safety alerts almost doubled from 19 in 2010, to 36 in 2012, and there have been 32 in just the first six months of 2013. This rise is indicative of FDA's wider reach and drive to identify issues of violation. Well-recognized companies including Apotex, Bausch & Lomb, Bayer, BMS, Cephalon, Genentech, Gilead, GSK, Greenstone, J&J, Mylan, Sandoz, Smith & Nephew, Teva, Watson and West Coast, have all been cited by FDA. Again, this list indicates both innovator and generic companies.

An increasing number of companies are attracted to and have a presence in the US market, but this means the numbers of inspections and defaults are also rising. However, what may be of greater concern, both to the drug regulators and the public health administrators, is that the list of defaulters contains established companies. Also of concern is the types of default that are on the rise. Violations of cGMP may be related to packaging errors, equipment cleaning and sterility issues, but more than one-third of reported incidents relate to "undeclared ingredients" and "unapproved drugs". This suggests a willful attempt to bypass regulatory oversight, and in these cases the responsibility rests squarely with the pharmaceutical industry. It is noteworthy that these incidents declined somewhat between 2010 and 2012, but have risen again during the first half of 2013.

A third major concern relates to the rapid increase in the detection of foreign particles in drugs. A common problem, this isn't a deliberate violation, but needs to be addressed, with the help of guidance from the regulators and experts.

Many other issues could be similarly resolved, but it will require a change in how the role of drug inspectors is perceived: less as a forensic auditor, and more as a guide, to help ensure the common goal of ensuring safe, effective and quality medicines.

Attempts to Beat the System

So, if some of the major global companies haven't been able to keep pace with the frequent regulatory changes that govern drug quality and cGMP, there is no reason to believe that new entrants to the US market will be any better placed to overcome these challenges. From what the last few years' of data show, some of the smaller and relatively lesser known companies seem to be indulging in willful default, and it is likely that a large number of new companies that are attracted to the US market could perceive this as an opportunity, which will result in further attempts at deliberate default.

Technology will play a key role in making sure that an increasing number of violations, whether deliberate or not, are identified, for example, by enabling the more accurate detection of foreign substances in manufactured products. The upshot is that we may hear more of alerts, recalls and market withdrawals, unless the industry adopts a new culture and plays an active part in reducing such incidents.

Cultural Change And Communication

A number of questions are raised, however. Which are the areas that will present the greatest future regulatory risks and lead to the largest numbers of warnings, and how can we stop or minimize them as new companies rush into the US market without adequate preparation? The growing trend towards zero tolerance will necessitate changes in attitude and culture across an organization. The industry needs to become more introspective and look for ways to overcome these issues. Leave it up to the regulator, and the solution may involve scaling up the penalty for willful default. Companies from all geographies must embrace these changes, both horizontally and vertically, enterprise wide. It is a slow process that will require patience and perseverance, as many organisations pay attention to

manufacturing, but devote little effort to prepare the people for change.

Regulatory authorities and companies will also need to make more effort to communicate the rationale of the prescribed processes that are put in place. Expecting compliance without understanding is futile. The mitigation of risks requires much better appreciation of the drug safety rules and a clearer understanding of the processes.

Barriers to Market Entry

We also need to consider the types of regulatory changes that may take place, and their effects on the market. Current outcomes and practises indicate that the majority of warnings will stem from the North (US, Europe and China). Some of the past changes are already perceived as being directed towards raising technical barriers to competition from the low cost, efficient producers, and the regulators and technical experts constituting the International Conference on Harmonization (ICH) may continue to strive for perfection at the risk of ignoring the cost-benefit analysis. This could delay entry of follow-on biologics, and may lead to some marginal players giving up the US market, which will ultimately reduce competition.

Another point to consider is the need for and likelihood of increased regulatory integration, and the consequences of it not happening. Most companies, irrespective of their size, sector (originator or generic) and domicile would like to see greater integration of regulatory processes to reduce delays

and the associated costs of approval. However, while some cooperation between drug regulators in different markets is likely over the next few years, complete integration is unlikely in the near future. Some regulators may not be willing to give up their authority, and a push towards integration could also be met by barriers of sovereignty. It is thus likely that the industry will have to continue to have to negotiate regulatory delays and the cost of duplication.

Take all these points into consideration, and it's also likely that during the next five years, the regulatory landscape will push up the price of medicines as companies face ever-increasing costs of compliance, and these costs will price new companies out of US market, effectively reducing competition.

What's the Solution?

So what's the solution? Can independent auditors resolve all these issues? What should the FDA do? Independent auditors can only expose technical deficiencies and help overcome them every time they find them. The solution will have to come from within industry, through a change in culture and attitude. The regulator will play a role, through its willingness to share responsibility with the companies for issues such as cGMP-related failures, and the implementation of processes that could address causative issues. Rather than just policing the industry, the regulator will need to consider itself partly accountable for failures, and shift its role from one of purely inspection, to one of training.



PANEL MEMBER

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Implementing Health- and Science-Based Risk Assessment for Multi-Product Manufacturing

Summary of market predictions

- Aside from certain, designated products, many investigational medicinal products (IMPs) intended for clinical trials can be manufactured in multi-purpose facilities, as long as stringent cleaning processes are put in place between the manufacture of different products
- There has long been discussion about the need to apply more rigorous, product-specific criteria to assess the risks of manufacturing individual IMPs in multi-purpose facilities
- Industry will be moving to a more health-based approach to risk assessment within the next five years
- EMA has issued a draft guideline as the basis of a framework for assessing the risks associated with multi-product manufacturing of individual biologics using science- and health-based criteria, with input from a toxicologist
- Early phase IMPs for which there is insufficient toxicology data available to calculate risk values would have to be manufactured in a dedicated facility, which could slow or prevent some molecules entering clinical trials
- Fujifilm Diosynth Biotechnologies has developed a potency and toxicology-based framework that allows assessment of early phase IMPs when sufficient toxicology data may otherwise be unavailable or incomplete
- The approach assigns IMPs to bands based on the available safety data for the product itself and/or toxicology and potency information on products with a similar mode of action
- This science-based system could allow early phase IMPs with limited data to be manufactured in multi-product facilities, rather than automatically assigning them to manufacture in dedicated facilities

Introduction

During the last ten to fifteen years it has become common practice to manufacture biologics intended for clinical trials (Investigational Medicinal Products, or IMPs) in multi-purpose facilities, both in-house by pharmaceutical and biotechnology companies and increasingly, by the growing CMO (contract manufacturing organisation) sector. This flexibility has been one of the key enablers ensuring a flow

of novel products, frequently targeting areas of unmet or poorly met clinical need, through the global pipeline.

Historically regulators required some product types, including specific antibiotics, hormones, cytotoxics and certain highly active drugs, must be manufactured in dedicated or segregated self-contained facilities (EMA,

2009). Other products can, in principle, be manufactured in multi-product facilities, given appropriate controls.

In recent years there has been much debate amongst regulators and professional and trade organisations

centred on establishing a clearer definition of what can be manufactured in multi-product facilities, and developing a better science-based risk assessment framework (see Abromovitz et al, 2009; LeBlanc et al, 2012).

Draft Guidelines Could Prevent Some Biologics from Entering Clinical Trials

The EMA recently published its draft 'Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities' (EMA, 2012). This draft guideline is a significant step towards establishing such a rigorous framework for assessing the risks associated with multi-product manufacture. The move towards using health- and science based approaches to consideration of risk associated with product changeover in multi-product manufacturing facilities is a logical, prudent and important step forward that will have significant impact in the next few years.

However, if the guideline is adopted in its current form it could impose significant new constraints on how early phase IMPs, particularly biologics, are manufactured, and could require that each IMP be manufactured in a dedicated facility. This would clearly have a radical and damaging impact on the global development pipeline by slowing, and possibly preventing the movement of some biologics into early clinical trials.

This article explores some of these issues and makes proposals for a health-based approach founded on sound science, which could be used to consider safe and effective manufacture of early phase IMPs in multi-product facilities.

So What's The Problem?

In 2009 the European Medicines Agency (EMA) issued a ground-breaking note entitled 'Update on revision of Chapters 3 and 5 of the GMP Guide: "Dedicated facilities" (EMA, 2009)'. This pointed to a concept paper published in February 2005 highlighting the lack of clarity in the existing EMA GMP guide (section 6 chapter 3, sections 18, 19 chapter 5) on when a medicinal product should be manufactured in dedicated self-contained facilities, and proposed that any guidance should take into consideration the principles and concepts of Quality Risk Management as outlined in ICH Q9. The EMA update concluded: "The topic of dedicated facilities continues to be the subject of a significant amount of debate but the GMP/GDP Inspectors Working Group has agreed that the use of dedicated facilities should normally be required when beta-lactam antibiotics are produced. In addition dedicated facilities should be used when live pathogenic organisms are handled".

Very importantly, it also concluded that "In the meantime, for other products, manufacturers introducing a product

into shared facilities should carry out an assessment of all relevant product and process characteristics to evaluate whether it is suitable for production in shared facilities. This assessment should include input from a toxicologist. Where the product has known sensitizing potential, or is highly potent or toxic, the Supervisory Authority should be consulted to discuss the manufacturer's risk management measures". This advice covered pharmaceuticals, biologics and IMPs. A critical and new component in this advice was that the risk assessment should include input from a toxicologist.

In 2010 the International Society for Pharmaceutical Engineering (ISPE) published its Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP) (Abromovitz et al, 2010). This sought to provide a scientific risk-based approach, based on ICH Q9, to the management of cross-contamination risk, which would allow the selection of appropriate risk control strategies to maintain patient and operator safety and assure product

quality. The Risk-MaPP framework had input from a wide range of companies and was shared with major regulators before publication. Its core recommendation is the use of a number of risk-based approaches and adoption of the health-based concepts of toxicologically determined Acceptable Daily Exposure (ADE) and Operational Exposure Limits (OEL) to control cross contamination exposure to patients and operators, respectively.

In December 2012 the draft EMA guideline (EMA, 2012) recommended use of Permitted Daily Exposure (PDE) or the

Threshold of Toxicological Concern (TCC) parameters when considering the production of different medicinal products in shared facilities.

The definitions of the health-based limits ADE and PDE are described in Figure 1. They are essentially similar and aim to define a daily dose of a substance below which no adverse effects are anticipated if individuals are exposed to the molecule each day for a lifetime. They are derived from toxicological studies and require professional toxicological expertise to determine.

Figure 1: Health-Based Limits

Acceptable Daily Exposure (ADE)

Daily dose of a substance below which **no adverse effects** are anticipated, by any route, even if exposure occurs for a lifetime:

$$ADE = \frac{NOAEL (BW)}{(UF_c) (MF) (PK)}$$

expressed as mg (or µg) per day. Where

NOAFL = No Observable Adverse Effect Level (mg API/kg body weight)

BW = Body Weight (kg)

UF_c = A composite safety factor determined from factors such as inter and intra species differences, subchronic to chronic extrapolation, LOAEL to NOAEL extrapolations and database completeness

MF = Modifying factor based on the judgement of a toxicologist

PK = Pharmacokinetic Adjustments

Permitted Daily Exposure (PDE)

The PDE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose everyday for a lifetime:

$$PDE = \frac{NOAEL (BW)}{F1 \times F2 \times F3 \times F4 \times F5}$$

F1: A factor (values between 2 and 12) to account for extrapolation between species

F2: A factor of 10 to account for variability between individuals

F3: A factor of 10 to account for repeat-dose toxicity studies of short duration, i.e., less than 4-weeks

F4: A factor (1-10) that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity

F5: A variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

For product A to product B considerations Maximum Allowable Carry Over (MACO) calculations then use ADE or PDE as the constraining allowable carryover.

A great advantage of using this approach is that it does not require imprecise definition of a molecule as 'highly potent' or 'toxic' when determining whether certain control measures are required. Rather, these flow from the ADE or PDE calculated and any associated product-to-product carryover, e.g. maximum allowable carry-over (MACO) calculations. These approaches work well for launched

products and late phase IMPs where the toxicological data needed to enable derivation of ADE or PDE is available, and where likely doses of products are known.

Historically, manufacturers making biologics in multi-product facilities have not used health-based cleaning limits when considering product-to-product changeover.

Two approaches have been most commonly used:

- i. Cleaning to industry recognised defined limits (e.g. visually clean and <20ug TOC/25cm², 1ppm TOC) (LOD or LOQ) etc.
- ii. Cleaning to <1/1000 dose or 10ppm of product A carrying over to product B

The proposed health-based exposure limit method of risk assessment has many advantages over the approaches mentioned above, and our company has been utilising ADE-based assessment for several years when considering product-to-product changeover.

So Why is a Health-Based Limits Approach Problematic for Some IMPs?

The EMA draft guideline (EMA, 2012) concludes that: 'In cases where scientific data does not support threshold values for safety (e.g. allergenic potential from highly sensitising materials) or where the risk cannot be adequately controlled by operational and/or technical measures, dedicated facilities are required for manufacturing of these high-risk medicinal products...' (lines 45-470) phase.

The ADE/PDE approach is problematic when used with some early phase IMPs, particularly biologics, as a number of parameters are frequently not known when decisions to proceed to manufacture are taken. Important examples include:

- i. For some early phase IMPs there may be no or little toxicological information available to enable the calculation of an ADE. Companies developing such molecules often require the manufacture of early GMP batches before toxicological studies have been completed, as they often use the same early batches of GMP product for toxicological and early clinical studies.

- ii. For many early phase IMPs the intended dosages of the product (product A) and subsequent product (product B) may not be known at the point of manufacture, thus preventing meaningful MACO calculations.
- iii. Decisions to manufacture IMPs are often made before information relating to the identity of subsequent products in the manufacturing assets is known.
- iv. Highly sensitive product-specific assays (more sensitive than TOC-based assays) are frequently not available at the early phases of product development and in practice are often not available until late clinical phase.

These factors may make it impossible to calculate an ADE or PDE for an early phase IMP because the data required are simply not available. It would then be impossible to perform MACO calculations because the doses of products A and B may not be known. Does this mean that a novel IMP should be manufactured in a dedicated facility? If so, many developmental products will never make it to clinical trials.

Towards a Solution: Potency Toxicity and Banding

There has been a general view that biologics, being largely protein-based are not, as a class, toxic. This view is supported by studies demonstrating that biologics have a significantly lower failure rate than small molecule pharmaceuticals in safety- indicating clinical trials. (DiMasi et al, 2010). Biologics are typically proteins of ~5-100kDa molecular weight, and they are generally water-soluble. Their biological activity is determined by their three-dimensional shapes, which it is

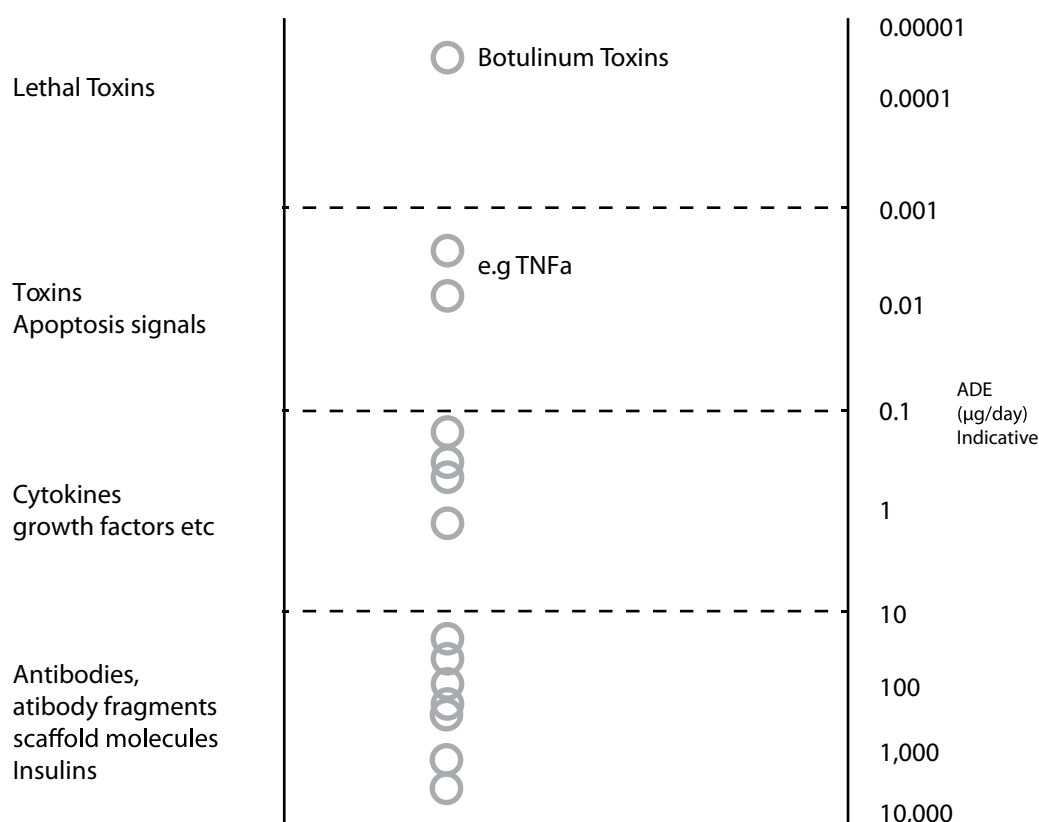
assumed are easily degraded by the cleaning chemistries used in industry. Such molecules are usually quite specific in biological effect and are frequently of low general toxicity. Some biologics are highly toxic because of their biological function (e.g. botulinum toxin), but this is rare.

The use of health-based exposure limits, however, does not differentiate between concepts of toxicity and potency,

and the recognition that, whilst proteins may not be toxic many of them are highly potent, is leading towards a change of view about how such molecules are manufactured and handled.

Biologics as a class of molecule exhibit a wide range of potencies, and a number of them are highly potent. The range of potencies displayed by biologics expressed as ADEs is shown in Figure 2.

Figure 2: Potency of Biologics (Recombinant Proteins)



n.b. ADE values and banding boundaries are indicative and are only presented for illustrative purposes.

From this it can be seen that certain subclasses of biologic molecules, e.g. monoclonal antibodies and cytokines, tend to lie in different parts of the potency spectrum. So, for instance, most interferons have similar ADE values, and these are distant from most monoclonal antibody ADE values. This grouping is useful as it may allow experienced toxicologists and scientists to make some assessment of the potential potency of molecules even when there is insufficient information to enable full calculation of an ADE or PDE.

Fujifilm Diosynth Biotechnologies has developed a framework that allows the use of health-based assessment for early phase IMPs when relevant data may be unavailable or incomplete. We would propose that the approach required by the draft EMA guideline is applied where there is sufficient data to derive a PDE or ADE and perform MACO or similar calculations, but for early toxicology/Phase I materials where such data is not available, a Banding approach be considered, similar to that widely used in the Health and Safety environment for deriving Occupational Exposure Bands (OEBs).

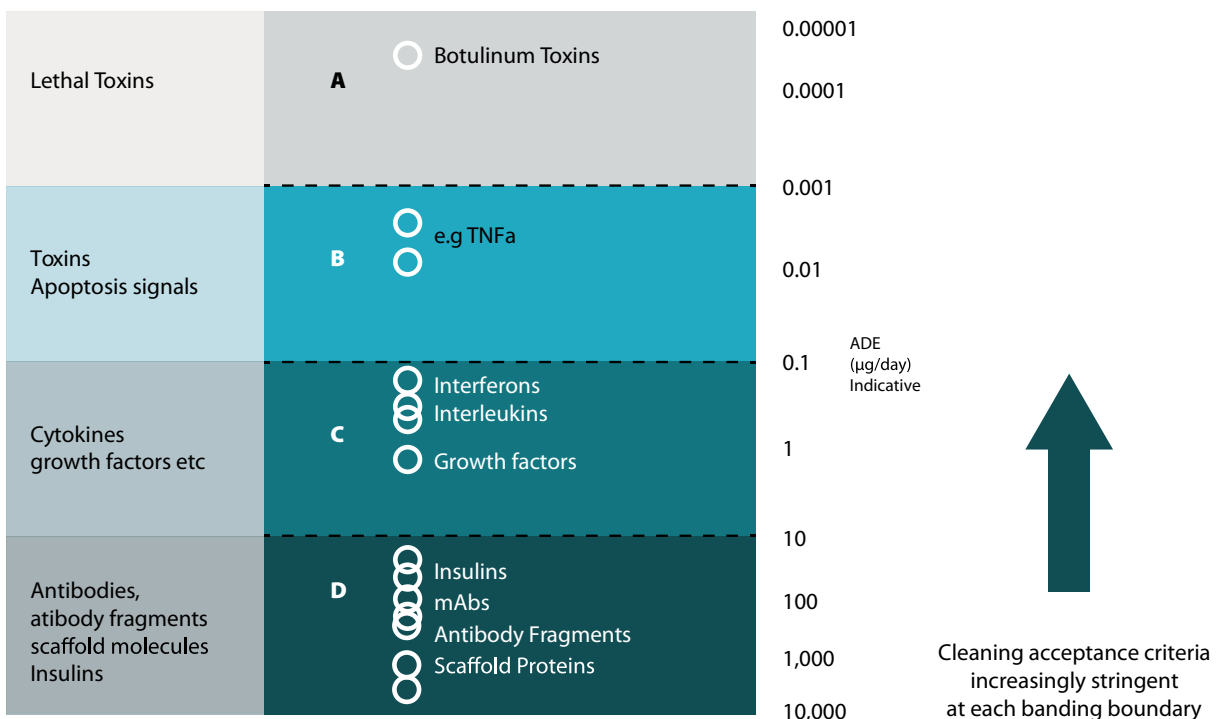
The value of classifying chemicals into OEBs according to their hazards has been recognised for many years. Systems developed by a number of major pharmaceutical companies in the late 1980s classified compounds based on the severity of hazard, and the controls required to reduce exposures to acceptable levels is described in an American Industrial Hygiene Association (AIHAJ) article (Naumann et al., 1996). Around the same time that banding schemes were being discussed in the US, the Association of the British Pharmaceutical Industry (ABPI) published a similar hazard categorisation scheme (ABPI, 1995). Meanwhile, the Health and Safety Executive (HSE) in the UK was developing a user-friendly banding scheme called COSHH Essentials (Brooke, 1998; Gardener and Oldershaw, 1991; HSE, 1999; Maidment, 1998). The International Labor Organization is also supporting the use of control banding throughout the world, especially in less-developed countries.

Fujifilm Diosynth Biotechnologies is recommending that the same concept should be applied to the toxicology assessment for early phase APIs. Where the level of

information cited in the EMA guideline isn't available we would recommend a qualified/certified toxicologist be permitted to assign a band based on the available safety data for the product itself and/or information on products with a similar mode of action. The level of uncertainty in the assessment would be factored into the Band assignment, with those with the highest level of uncertainty defaulting to a higher risk Band.

A series of 4-5 Bands is recommended, each with an expected ADE or PDE range. The lower end of this range for a given Band (i.e. worst case) could be used to calculate permitted carryover limits for equipment residues. The Band assigned would also define the scope of the risk mitigation required, for example, where equipment should be dedicated, single-use equipment should be substituted for reusable equipment, and/or where the entire processing scheme should be configured in an enclosed processing train. Assignment to certain bands could be set to automatically require use of fully dedicated facilities. Figure 3 outlines an indicative banding approach for illustrative purposes.

Figure 3 : Potency of biologics – possible 'banding' scheme



n.b. ADE values and banding boundaries are indicative and are only presented for illustrative purposes.

Fujifilm Diosynth Biotechnologies recommends that each firm generates its own banding scheme and associated controls based on the facility and risk assessments, and similar to the approach taken in the Health and Safety models. The risk associated with not being in a position to assign an acceptable carryover limit at the time of manufacture of a product, in the absence of information on the identity, batch size and/or dose of the next product into the equipment, could be mitigated by ensuring that a

maximum allowable carryover calculation (MACO) is carried out as part of each new product introduction to confirm that the carryover limits determined are higher than the verified residue levels post cleaning. In the event they were not, the equipment could not be shared with the follow-on product. These considerations have been implemented in the manufacture of small-molecule pharmaceuticals that are designated as potent molecules (EU Directive 89/391 EEC).

Towards a Solution: Potency Toxicity and Banding

Aside from certain, specified biologic IMPs that must be manufactured in dedicated or self-contained manufacturing facilities, many investigational products can be manufactured in multi-purpose facilities, as long as validated cleaning procedures are put in place to minimise the risk to personnel and patients of carryover. Debate and discussion among regulators and the industry will lead to changes over the next five years in the way that these assessments are carried out. The move is now towards the use of health- and science-based approaches to calculating the risks associated with manufacturing individual IMPs in multi-purpose manufacturing facilities.

However, a recent draft EMA guideline, if adopted in its current form, could slow and possibly prevent some biologics from moving into early clinical trials, by forcing their

manufacture in fully dedicated assets due to lack of sufficient toxicology information.

Even when there is only partial data on early phase developmental products and the likely doses they will be used at to support full PDE and MACO type calculations, there is often sufficient information to allow good science- and health-based risk judgments to be made if frameworks such as the banding approach we propose are adopted. Further careful consideration and exploration of this challenge by all interested parties is required.

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