Future of clinical trials in Germany and impact of Brexit

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THERE'S a real concern that regulatory uncertainty and delays at borders after a "no deal" Brexit will result in shortages of approved medicines which are shipped freely without any trade barriers across the UK and EU.

According to the press release in Feb 2019, Germany's Federal Institute for Drugs and Medical Devices (BfArM) has warned that it could suspend 1,300 clinical trials in the event of a no-deal Brexit.

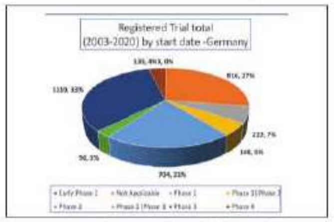
The warning reflects the fact that the sponsors of many studies are still registered in the UK and there are stipulations in the Medicinal Products Act (AMG) about who can run trials in Germany. Clinical trials of non-German sponsors i.e. UK are allowed only on a conditional basis by the Germany's clinical trial regulatory act (AMG) and subject to the agreement on the European Economic Area.

Under AMG, BfArM will then be legally obligated to order the suspension of clinical trials sponsored by the UK-based organisations.

The drug development industry also faces real problems if Brexit goes through. If companies can't deliver materials used in ongoing clinical trials, then there's a risk that patients could miss doses. Of course, this could delay regulatory approvals, but for the individual patients enrolled in trials, it could have serious immediate consequences.

For example, for patients enrolled in late stage oncology trials that are really relying on the investigational products, missing a shipment and a patient dosing can be a major disaster for the patient. The clinical supplies industry, from sponsors to clinical supplies organisations, are working continuously to finding ways to make sure this does not happen as a result of a 'no deal' Brexit."

Moreover, with the prevailing uncertainty on the "No Deal Brexit", sponsor companies of clinical trials are now exercising caution with trial registration in the European union countries particularly in Germany. This ongoing uncertainty is the primary reason for the "slowdown" of clinical trials in Germany since the last decade.



Phase wise clinical trial classification in Germany (2003-2020)

Phase 2 and phase account for nearly 50 per cent of Germany's clinical trial market since the last 17 years.

Around 27 per cent of clinical trials are also in the "not applicable" category. This category mainly features clinical trial intervention in the diagnostic, procedural, device, device training, behavioural training and mostly related to non-invasive clinical trial activities in Germany. This trend is gradually on the rise on account of the changing face of the population, less hurdles in regulatory approvals, etc. The trends in the "not applicable" category clinical trials have witnessed an incremental growth of 50 to 80 trials per year since the last five years.

Germany registered trials by Funding type -Trends	2012	2013	2014	2015	2016	2017	2018	2019	Grand Total
Industry	48	109	133	239	253	394	455	377	[illegible]
Other	30	38	56	93	128	180	220	164	580
Other Industry	13	6	19	33	38	35	44	29	225
Grand Total	95	[illegible]	219	377	[illegible]	[illegible]	738	[illegible]	3355

Note : Funding type categories account for 95 % of the total trials since 2003

Trends in clinical trial funding in Germany

Industry sponsored clinical trial growth in Germany doubled by nearly 100 per cent in the year 2015 over 2014 and remained steady till 2016. From the year 2016 onwards, nearly 60-100 trials have been registered year on year. Industry sponsored trials account for more than 60 per cent of the total registered trials in Germany.

Clinical trials in Germany are also classified in to registered trials which are active and recruiting, recruiting, active but not recruiting, Not yet recruiting and recruitment by invitation.

Out of the above categories, recruiting trials are the highest (Total=1991) out of the 3355 registered clinical trials in Germany. Non-Invasive trials (diagnostic, procedural, training oriented, etc) show a rising trend in active recruitment since 2012 in the "not applicable" category. The number of clinical trials in terms of recruitment status are the second highest as a trend for Phase 3 since the year 2012. Phase 2 clinical trials ranks third in registered clinical trials by recruitment rate in the yearly trend since 2012.

Trends in registered clinical trials in Germany by enrolment criteria

The total number of registered volunteers in all phases of clinical trials in Germany from the year 2003 to 2019 has crossed the 17-lakh mark. Nearly 10-lakh registrations of volunteers in clinical trials in Germany has taken in the Phase 3 clinical trials category starting from the year 2003. Five lakh registered volunteers feature in the "not applicable" category which involve diagnostic, procedural, training oriented, etc techniques. Registration of volunteers in this category of clinical trials is greater than One lakh per year since the year 2017. Phase 2 falls third in the list of total registered volunteers (1.25 lakh from the year 2003 -2019) for the total no of active participants in Germany.

Top sponsors in German clinical trial market

Top five sponsors in Phase 1 trials in Germany are Novartis (28), Boehringer Ingelheim(20), Bayer(10), Amgen (8), Janssen Research & Development(8), LLC, Hoffmann-La Roche (7) in the years starting from 2012 to 2019. This means the average registration of Phase 1 clinical trials in Germany since the last 7 years by the top five sponsors is less than five per year. Total number of registered clinical trials from the year 2015-2019 are 222. The top five sponsors account for 36 per cent (81) of the total registered phase 1 clinical trials in Germany.

Top five sponsors in Phase 2 trials in Germany are

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New rules designed to reduce administrative burdens

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Novartis (50), Bristol-Myers Squibb (19), Boehringer Ingelheim (14), Hoffmann-La Roche (14), Janssen Research & Development, LLC (13), Celgene (12), AstraZeneca (11) and Eli Lilly and Company (11). Total number of registered Phase 2 clinical trials in Germany are 709 from the year 2015-2019. The top five sponsors account for 20 per cent (144) of the total registered phase 2 clinical trials in Germany.

The largest number of registered clinical trails by sponsor falls in the Phase 3 clinical trial category where 1119 trials have been registered from the year 2012 -2019.

Top sponsors in the registered phase 3 clinical trials category are Hoffmann-La Roche (62), Novartis (61), AbbVie (40), Eli Lilly and Company (33), AstraZeneca (29), Bristol-Myers Squibb (26), Janssen Research & Development (24), LLC and Merck Sharp & Dohme Corp (24). Phase 3 is the only category of registered clinical trials in Germany where Novartis ranks second among the top pharmaceutical industry players. The top eight players account for 27 per cent (299) of the total registered phase 3 trails in Germany from the year 2012-2019.

Registered clinical trials in Germany

Top 11 Indications which feature among the registered trials in Germany are multiple myeloma, breast cancer, non-small cell lung cancer, atopic dermatitis, asthma, prostate cancer, ulcerative colitis, psoriasis, heart failure, melanoma and rheumatoid arthritis. These indications account for nearly 10 per cent of the total registered clinical trials in Germany from the year 2012-2019. A total of 2068 unique conditions feature in the registered clinical trials in Germany from the year 2012-2019.

Overall study design purpose of clinical trials in Germany

The overall study design purpose of clinical trials in Germany lies in the treatment category where 85 per cent of the total 3355 trials are registered from the year 2012 -2019. The remaining registered category of clinical trials in Germany fall under the non-invasive categories of Basic science, Device feasibility, Diagnostic, Health services research, Prevention and Screening.

Future of clinical trials in EU

The current clinical trial regime in the EU is due to be overhauled by the new EU Clinical Trials Regulation (No 536/2014). The new regulation will modernise the current framework for clinical trials and ensure a greater level of harmonisation within the EU. The new regulation, which provides for a single application for clinical trials across the EU via a single portal with an associated EU wide database, is designed to significantly reduce administrative burdens on applicants and allows for a simplified process where the investigational medical product poses less risk.

If the UK is not within this system, then this could pose extra administrative burdens on companies wishing to conduct multi-centre clinical trials in the EU and the UK. Separate centralised and national clinical trial authorisation procedures need to be followed. However, mutual recognition arrangements may be arranged to minimise any such inefficiencies brought about by Brexit. ◆